Chapter 12

The New Medical Device Regulation and In Vitro Diagnostic Device Regulation

By Gert Bos PhD, FRAPS and Erik Vollebregt, LLM

OBJECTIVES

- Gain insight into the revised European medical devices and IVD legislation
- Understand the major changes in these new regulations
- Become aware of the transitional regime and preparatory requirements for companies in the medical device and IVD industries

DIRECTIVES, REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER


Introduction

The EU has spent the last decade on a radical overhaul of its medical devices legislation. The new Medical Device Regulation (EU MDR) and In Vitro Diagnostic Device Regulation (EU IVDR) will provide a new regulatory framework for medical devices in the EU for the coming decades. They are constructed with a series of implementing and delegated legislation that will allow them to be revised and fine-tuned in almost every detail. In this way, the future will see incremental legislation rather than another massive regulatory overhaul. The first additional legislative pieces are expected to be introduced in late 2017 or early 2018.

The proposals were initiated in 2007 and finalised in 2012, after which a number of years of political and technical debates followed until their final publication in Q2 2017.

The EU MDR will replace the existing Medical Devices Directive (MDD, Directive 93/42/EC) and Active Implantable Medical Devices Directive (AIMDD, Directive 90/385/EEC), while the EU IVDR will replace the IVD Directive (Directive 98/79/EC).

Essential in the legislative reform is that it will form a clearing house for all legacy products and operators. As such, there intentionally is no grandfathering for products already CE-marked, and no grandfathering for Notified Bodies.

Why a new EU MDR and EU IVDR?

The revision of EU medical devices law began in 2007 with informal interactions between the EU Commission and selected stakeholders, followed by two more formal consultations in 2008 and 2010 that aimed to make mid-life updates to the existing directives for medical devices, active implantable medical devices and IVDs. The oldest of the three directives dates back to 1990 and never has been changed substantially.

In 2012, when the Commission made its legislative proposals, it felt compelled to amend them significantly following an additional impact assessment related to several highly publicised issues with medical devices in the EU market, such as the PIP breast implants, metal-on-metal hip
implants, pelvic floor meshes, etc., which sparked a political wish for more centralised and premarket controls on higher-risk medical devices. These issues impacted the EU MDR proposal debates heavily and led to much divergence on subjects among both the involved political institutions and Member States.

The EU IVDR proposal was influenced less by external issues, but in many respects followed the EU MDR path.

Scope of the New EU MDR and EU IVDR
Since both regulations are intended to account for technological developments, both feature a considerable extension of scope compared to the directives they will replace. In addition, in many places, the phrase ‘state of the art’ is used, sometimes in comparison to the practice of medicine. In this way, the interpretation of acceptable risks will ensure gradual replacement of older products with more-modern medical devices.

EU MDR
The proposed EU MDR extends its scope not only to devices currently not regulated as medical devices. It also includes devices for which the manufacturer does not claim an intended medical purpose but have a risk profile similar to medical devices, such as contact lenses, cosmetic implants and invasive laser equipment. These devices will be included on the so-called Annex XVI list, which the Commission may amend over time to include additional devices.

The EU MDR will absorb the AIMD. Active implantable devices currently regulated under that directive will fall within the EU MDR’s highest medical device risk class, including their accessories that automatically will be Class III, in contrast to other medical devices’ accessories that are classified in their own right. This integration ends the old adage in which the original intent was to write a series of product category-specific laws on active implants, orthopaedic implants, cardiovascular implants, etc.

The EU MDR also includes a borderline decision mechanism to allow the Commission, through the new Medical Device Coordination Group (MDCG), to take binding decisions on product qualification, which the Commission presently cannot do.

Products manufactured utilising nonviable human tissues or cells (and their derivatives) will be regulated under the EU MDR, which has been a longstanding regulatory gap under the MDD. This will end the era where such products’ manufacturers had to negotiate the marketing approval path separately with each EU country.

EU IVDR
The EU IVDR includes a new regime for laboratory-developed tests (home brew tests) and companion diagnostics.

The EU IVDR provides specific definitions and regulatory requirements for ‘devices for self-testing,’ ‘devices for near-patient testing,’ ‘single-use devices’ and ‘kits.’

Accessories
The definition of accessory changes to incorporate devices that ‘assist’ a medical device in both regulations. This is expected to expand the scope of accessories covered by the regulations significantly, for example, with respect to networked or connected equipment and modular software.

Products specifically intended for cleaning, disinfecting or sterilising medical devices, and devices for controlling or supporting conception are treated separately as though they were medical devices, rather than as the accessories often claimed today.

Implementation of the MAID Goods Package
The MAID acronym refers to the medical device Manufacturer, Authorised Representative, Importer and Distributor, i.e., the economic operators covered by the new supply chain regime. Both regulations will implement the supply chain controls (Figure 12-1) developed in 2008 for CE-marked products set out in Commission Decision 2008/768 and since implemented in other EU New Approach regulations. The regulatory logic behind this has been described in detail in the European Commission’s Blue Guide.

The supply chain controls provide independent regulatory responsibility of the respective MAID supply chain actors regarding device compliance and an obligation to check the previous supply chain link’s compliance.

Under the current system, only the manufacturer has regulatory obligations. The new obligations of importers and distributors will necessitate an update to existing distribution and supply agreements.

With regard to Authorised Representatives, the regulations incorporate the requirements from the existing MEDDEV guidance on Authorised Representatives and feature prescriptive minimum requirements on the Authorised Representative mandate’s contents. Also, the regulations include an independent liability for defective devices within the scope of the Authorised Representative’s mandate, which in the early phase of implementation is indicated to be hard to ensure. This might well mean that companies will establish legal entities within the EU instead of using Authorised Representatives to ensure compliance with the new regulations.

Traceability
The EU will set up a traceability system under the new regulations that will assign unique device identifiers (UDIs) to all medical devices placed on the EU market, except custom-made and investigational devices. The system will
be part of the Eudamed system, the overarching EU IT architecture for administrating medical devices under the new regulations.

The regulations call for the Commission to promote interoperability among different UDI assignment entities and to minimise financial and administrative burdens for economic operators and health institutions. Currently, the EU’s UDI policy is to ensure the Member States do not set up systems that may conflict with the system contemplated under the regulations, and to ensure the finally agreed system under the regulation proposals is not incompatible with other UDI systems already in use in other countries. However, although more-detailed legislation is expected to be published in late 2017 or early 2018, several EU countries already have started to demand use of specific UDI systems for selected product categories as of summer 2018.

The manufacturer must assign a UDI prior to placing the device on the market. The UDI will be used for reporting serious incidents and field safety corrective actions and shall be included in the information to be provided to a patient implanted with a medical device.

Under the new regulations, Member States may require healthcare professionals and institutions to store and keep the UDIs of the devices with which they have been supplied.

The regulation proposals provide only general UDI requirements. The Commission will complete the modalities and procedural aspects to ensure harmonised application of the UDI System via implementing acts.

A provision is in place on how to comply with the new transparency rules if the new Eudamed system is not operational in time. It includes a period in which manufacturers retrospectively can fill the database once it goes live. That means manufacturers will need to start the UDI implementation at the specified times from 2021 onwards, and store all information until it can be embedded into the new EU database.

**Notified Bodies**

The EU will make considerable changes in Notified Body oversight, many of which stem from the Joint Action Plan currently being implemented to improve Notified Bodies’ quality. Notified Bodies not only will need to employ more expertise rather than hiring contractors, they also will play a role in enforcement by conducting unannounced inspections of manufacturing processes and taking a strong supporting role in following up vigilance reporting.

When the new regulations enter into force, all Notified Bodies will need to re-apply for accreditation under stricter rules, and the Commission also will play a role in the
accreditation decision. There will be no grandfathering of Notified Bodies into the new system. Currently, a minority of the Notified Bodies in the market are expected to be able to meet the new accreditation requirements with their current designated scope. This is expected to affect manufacturers, since they may need to change their Notified Bodies as a result.

Uncertainties about the Brexit negotiations’ outcome in terms of the UK continuing to be part of the EU single market means manufacturers now utilising British Notified Bodies might have to change twice over: first to the EU-based counterpart of their Notified Body (still under current directives) and secondly to move to EU MDR and/or EU IVDR certification.

**Market Access Mechanism**

The market access mechanism in general terms will largely stay the same, but the details will change radically.

Because of the political outrage over the PIP case, there has been a movement to increase premarket assessment of higher-risk medical devices. Initially, the Commission proposed a ‘scrutiny’ mechanism (Notified Bodies had to elevate the review of certain high-risk devices to specialized EU review committees). Parliament proposed a premarket assessment program similar to the US Food and Drug Administration’s (FDA), supervised by the European Medicines Agency (EMA). The Council proposed leaving the system as it is but adding the option of a scientific advice-like procedure by a specialised EU committee, where the manufacturer can validate in advance the clinical evidence required for market access. These are very different solutions for the same problem during the trilogue negotiations.

The market access system for low- and medium-risk medical devices will stay the same and see little change. For IVDs, there will be a quantum leap in all requirements. Currently, 10–20% of all IVDs in the EU are CE-certified; self-certification applies to the rest. Under the new regime, 80–90% of all IVDs will need to be CE-certified by a Notified Body, and self-certification will be possible only in limited cases for low-risk devices. This is resulting from IVD classification rules being introduced in the EU IVDR (see Figure 12-2) and discontinuing the current list-based classification system.

An additional challenge is that current IVD Notified Body staff have been selected based on their qualification for current list A and list B devices. With the much broader scope, Notified Bodies will need to hire additional staff with the relevant product design or production experience, as they might well lack sufficient regulatory knowledge to get started directly on conformity assessments.
Clinical Evidence, Clinical Trials and Regulatory Compliance

Clinical evidence is one of the core themes in both regulations due to the political wish to increase the amount of clinical evidence required to support a medical device’s safety and performance.

Both regulations contain comprehensive and detailed regimes for collecting clinical evidence (both pre- and post-market) using the existing MEDDEV guidance documents (e.g., the MEDDEV on postmarket clinical follow-up). The new regulations will require manufacturers to collect more clinical evidence than currently is needed, meaning manufacturers will need to start preparing for increased clinical evidence requirements for devices to be CE-marked under the new regulations. However, since the regulations will not ‘grandfather’ existing devices, manufacturers also must plan to collect additional clinical evidence for devices already CE-marked because they will need to be recertified under the new requirements. And even existing data from clinical trials performed by the manufacturer itself under the MDD and AIMD will need to be re-evaluated to confirm the data have been collected and analysed consistent with the new EU MDR requirements.

Both regulations implement a centralised clinical trial regime for covered devices, modelled on the EU medicinal product clinical trial regime. This includes notification in a centralised database that will be part of the Eudamed system. Initially, this will continue with a country-by-country approval on clinical trial initiation, but from 2027 onward, a central approval of a multi-country clinical trial will be in place. Until then, countries may experiment with multi-country approvals, following the details laid out for the 2027 system.

Due to the political desire to synchronise regulatory concepts pertaining to clinical investigation between the medicinal product and medical device regulatory frameworks, the legislative process has introduced important concepts inconsistent with the current EU harmonised Good Clinical Practice (GCP) standard for medical devices (EN ISO 14155:2011). For example, the EU MDR’s proposed definition of ‘sponsor’ is much broader than under EN ISO 14155:2011. Inconsistencies between the final regulations and the GCP standard may make the EU a less attractive clinical investigation location, and it is hoped the ISO standard will be revised to match the new EU expectations.

The regulations aim to increase companies’ regulatory awareness levels by obliging their organisations to have at least one available ‘person responsible for regulatory compliance.’ This will apply to both manufacturers and Authorised Representatives, except micro-enterprise manufacturers of custom-made devices. The responsible persons’ qualification requirements are set out in the regulations. This individual is, among other things, responsible for managing technical files, the Declaration of Conformity and reporting obligations. This individual is not required to be an employee but must be ‘available to the organisation,’ and, in specific circumstances such as is the case with large manufacturers, the assignment may be distributed over several people.

Postmarket Surveillance and Vigilance

Effectively starting in 2013, national Competent Authorities have begun to increase and coordinate market surveillance activities as part of the Commission’s Joint Action Plan. In addition, Notified Bodies have been obliged to start performing unannounced audits of manufacturers’ production processes, a process that took until sometime in 2014 to start, but now is in full swing.

The proposed regulations build on this development and introduce the following:

- incorporating the MEDDEV 2.12 Rev 8 vigilance system in regulation
- vigilance reporting of serious incidents and field safety corrective actions in the Eudamed system
- Periodic Safety Update Reports (PSURs), an inheritance from the EU pharma legislation
- centralised evaluation of the same or similar incident occurrences, or where more than one Member State has had to take a corrective action
- Member State cooperation under the Commission’s auspices (MDCG) to coordinate enforcement activities in a new electronic surveillance system and draw up ‘strategic surveillance plans’ to which the Commission may recommend changes
- binding procedure for dealing with noncompliant and compliant devices, both in national and cross-border situations; the Commission will function as an arbitrator between Member States with respect to provisional measures taken

Classification and Conformity Assessment

A new aspect of both regulations is the Common Specification adoption mechanism for general safety and performance requirements, technical documentation, clinical evaluation and postmarket clinical follow-up or clinical investigation requirements for specific devices or device groups. Common Specifications may be adopted by an implementing act if no harmonised standards exist or if relevant harmonised standards are insufficient. Adopting similar measures (common technical specifications) already is possible to a certain degree under the existing directives but, in practice, has been used only rarely under the IVDD. The Commission is expected to rely on Common Specifications much more under the new regulations. In addition, a new system of product-specific guidance documents is under development.
**EU MDR**

The EU MDR classification and conformity assessment procedures are staying largely the same, but details will be updated. An example is new rule 21, which will up-classify substance-based medical devices considerably (e.g., creams) absorbed by or locally dispersed in the human body. If they are intended to be introduced into the human body via a body orifice, they will be in Class III or IIb, and if applied on skin, they will be in Class IIa. For such substances, a special consultation with drug agencies might be needed.

A second example of key reclassification is in the special article of software, Rule 11. Also, software sees a stratified classification system, where most standalone software will be Class IIa or higher.

Thirdly, following earlier reclassification of selected orthopaedic implants, the new rules change most orthopaedic implants into Class III now. Exceptions exist for a list of long available 'simple’ products, where clinical data is not required.

As a last example, reusable surgical tools are being reclassified to a new Class Ir. As many such tools are made available by the manufacturer as a service, getting them certified, including the processes of returning, cleaning, sterilisation and redistribution, will have a significant impact.

**EU IVDR**

The IVD conformity assessment system will not change radically, but the IVD classification system will. The current list-based system will be discontinued in favour of GTHF's proposed system of four risk classes (A–D). Therefore, the classification rules will require 80–90% of IVDs to be CE-certified by a Notified Body because all except those in Class A will require Notified Body CE certification.

**Own-Brand Labelling Consequences, Reprocessing**

The regulations will have far-reaching consequences for two *capita selecta*, own-brand labelling (OBL) and single-use device reprocessing.

**OBL**

The widespread practice of OBL likely will be impacted by the new regulations. Each manufacturer will be obliged to have a full technical file available for the authorities, while the current legislation only requires an abbreviated technical file referencing the underlying original device’s technical file to be available to the authorities. Existing OBL schemes will have to be updated to enable each and every OBL manufacturer to have full access to the entire underlying technical file. As such, the guidance on changing OBL to virtual manufacturing recently published by the UK MHRA provides some good background.

**Reprocessing**

Single-use medical device reprocessing has been the most hotly debated EU MDR item, since it currently is not harmonised under EU law (apart from limited labelling requirements) and is left to Member States’ individual decisions. Also, countries have very different perceptions, based on scientific views and economic and social-cultural arguments.

After many arguments back and forth, the European regulations allow national decision makers to continue with their practice, but once they decide to allow reprocessing of single-use devices, they must follow a common conformity path.

**Governance**

The governance model is a combination of the various proposals the three EU institutions involved in the process have proposed:

- A Medical Device Coordination Group (MDCG) will be established, composed of Member State delegates with medical device and IVD expertise and chaired and supported by the Commission, which decides on consensus or majority vote basis.
- The MDCG will have certain tasks related to the EU MDR and EU IVDR centralised competences, e.g., assessing applicant Notified Bodies and their periodic accreditation renewals; involvement in high-risk device conformity assessments; developing guidance to ensure effective and harmonised regulation implementation; overseeing expert panels and expert laboratories advising the MDCG; and developing the EU market surveillance program.
- The MDCG will be consulted on many of the delegated and implementing acts the Commission will take to implement the regulations on such details as UDI and the Eudamed database.
- The MDCG will be consulted on applying EU procedures to deal with noncompliant devices.

The above makes it clear, whatever the governance model may be, EU medical device policy governance will be much more centralised and coordinated.

An overview of the governance structure can be found in Figure 12-3.

**Delegated and Implementing Acts**

The EU MDR and EU IVDR rely heavily on the Commission finalizing details by delegated competence to adopt so-called delegated and implementing acts. These acts are intended to enable the Commission to propose detailed implementing regulations on nonessential elements. In practice, however, these acts concern many important elements where the draft regulations lack considerable detail, such as the Notified Bodies' designation detail, the UDI and Eudamed systems.
the Annex XVI list of nonmedical devices regulated under the EU MDR and the EU model of the certificate of free sale. Also, the Commission is entitled to change the regulations’ technical aspects via delegated acts if it does not deem international standards compliant with EU law, e.g., the essential safety and performance requirements in EU MDR and EU IVDR Annex I, the conformity assessment procedures and common specifications to provide technical requirements.

Currently, it is unclear whether EU law permits companies to challenge implementing and delegated acts at the European General Court, even if these acts affect them directly.

**Timeline for Adopting the Regulations and the Transitional Regime**

Many companies are under the impression the new regulations’ entry into force will not affect devices already CE-marked. But beware, the regulations purposely do not allow any grandfathering, which means all devices CE-marked before the date of entry into force of the new regulations will need to be CE-marked again under the new regulations’ requirements. This means, among other things, a company may need to produce additional clinical evidence and have to redraft its technical files to meet the technical documentation format prescribed under the new regulations.

The transitional period between the regulations’ entry into force and date of application is three years for the EU MDR, and five years for the EU IVDR, although a soft transition scheme to prolong to a maximum of seven years is foreseen; however, in such a case, significant EU MDR elements already will be required, and the soft-transition is available only to products with an ongoing MDD, AIMD or IVD certificate that remains under the old Notified Body's scrutiny; no significant changes will be allowed in this time. Both regulations will feature a so-called sunshine compliance regime, meaning companies, from the date of entry into force, may comply with the new rules before the end of the transitional period. Prospective compliance may be difficult however, as the Commission is expected to be in the process of adopting delegated and implementing acts during the transitional period.

What will happen with existing CE certificates after the regulations enter into force? Certificates issued under the existing directives remain valid until the end of the period indicated on the certificate, except certificates issued for conformity assessment pursuant to EC verification (Annex 4 Directive 90/385, Annex IV Directive 93/42 and Annex VI Directive 98/79 respectively); these will be void, at the latest, two years after the transitional period ends.

CE certificates issued by Notified Bodies after the regulations’ entry into force (i.e., during the transitional period) also will be void, at the latest, two years after the transitional period ends (EU IVDR) or four years after (EU MDR).

Self-declared CE marking is not subject to the transitional regime for Notified Body-issued CE certificates. Manufacturers of self-certified devices will need to update
their declarations of conformity by the transitional period’s end but are allowed to do so as of the date of entry into force.

Summary

• The EU MDR and EU IVDR will change EU medical devices regulation profoundly in many areas, such as an enlarged scope of devices included under the rules, amended conformity assessment procedures and increased postmarket clinical follow-up and surveillance requirements.
• Companies will need to plan to generate more clinical evidence for medical devices and for new approval pathways for high-risk devices.
• Devices already CE-marked cannot be grandfathered and must be recertified under the new requirements.
• Notified Bodies are not grandfathered in, so manufacturers need to ensure they are working with a Notified Body that will obtain designation status under the new regulations for their product categories.
• The EU MDR and EU IVDR will include a centralised EU governance system to oversee medical devices, using a single IT system for collecting and sharing information; companies will need to interact with the system for registrations and notifications.
• The EU MDR and EU IVDR will provide a centralised clinical investigation system for medical devices and IVDs.
• The EU IVDR will require approximately 80–90% of all IVDs to be CE-certified by a Notified Body, compared to 10–20% under the current IVDD.

References


Recommended Reading