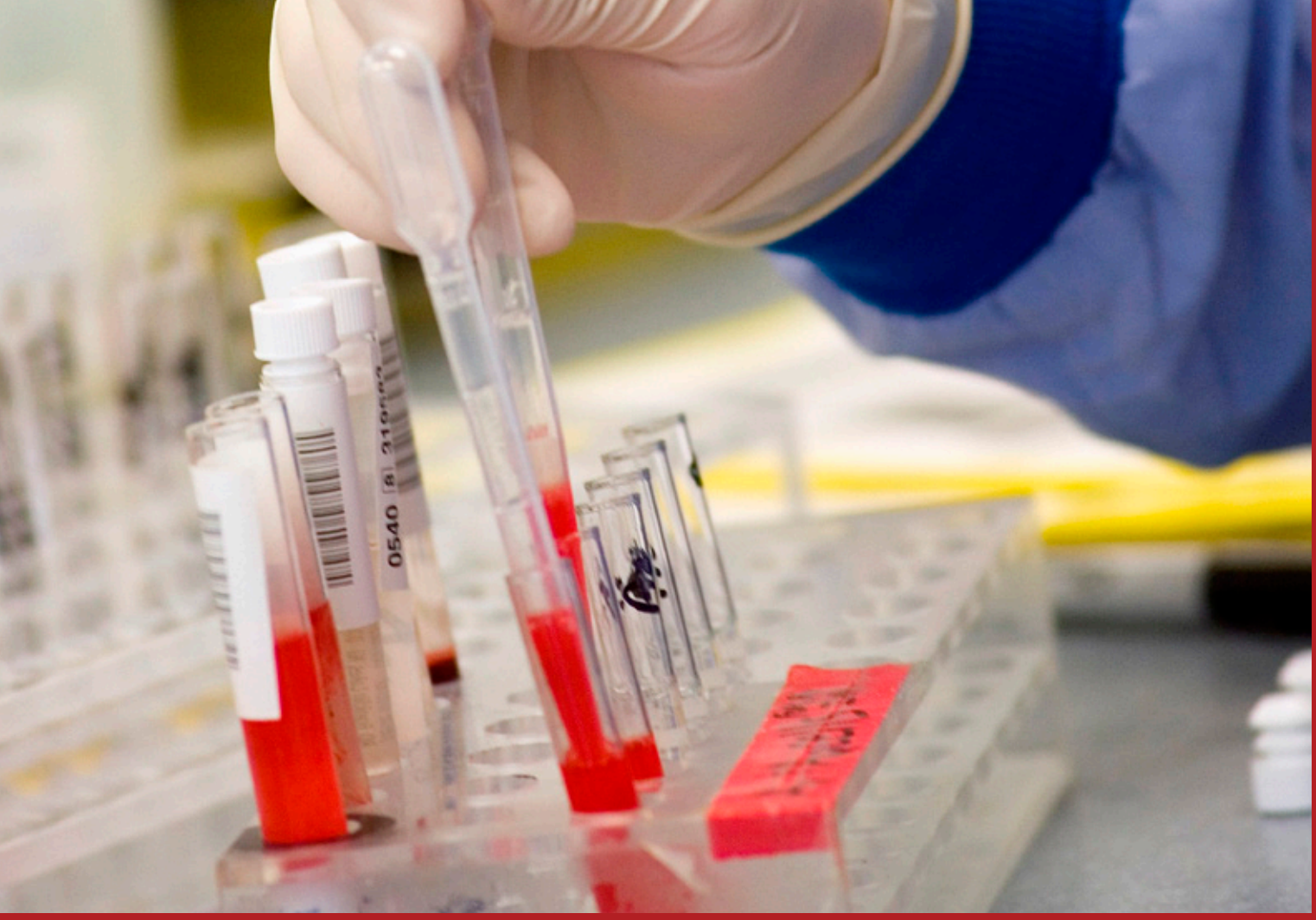


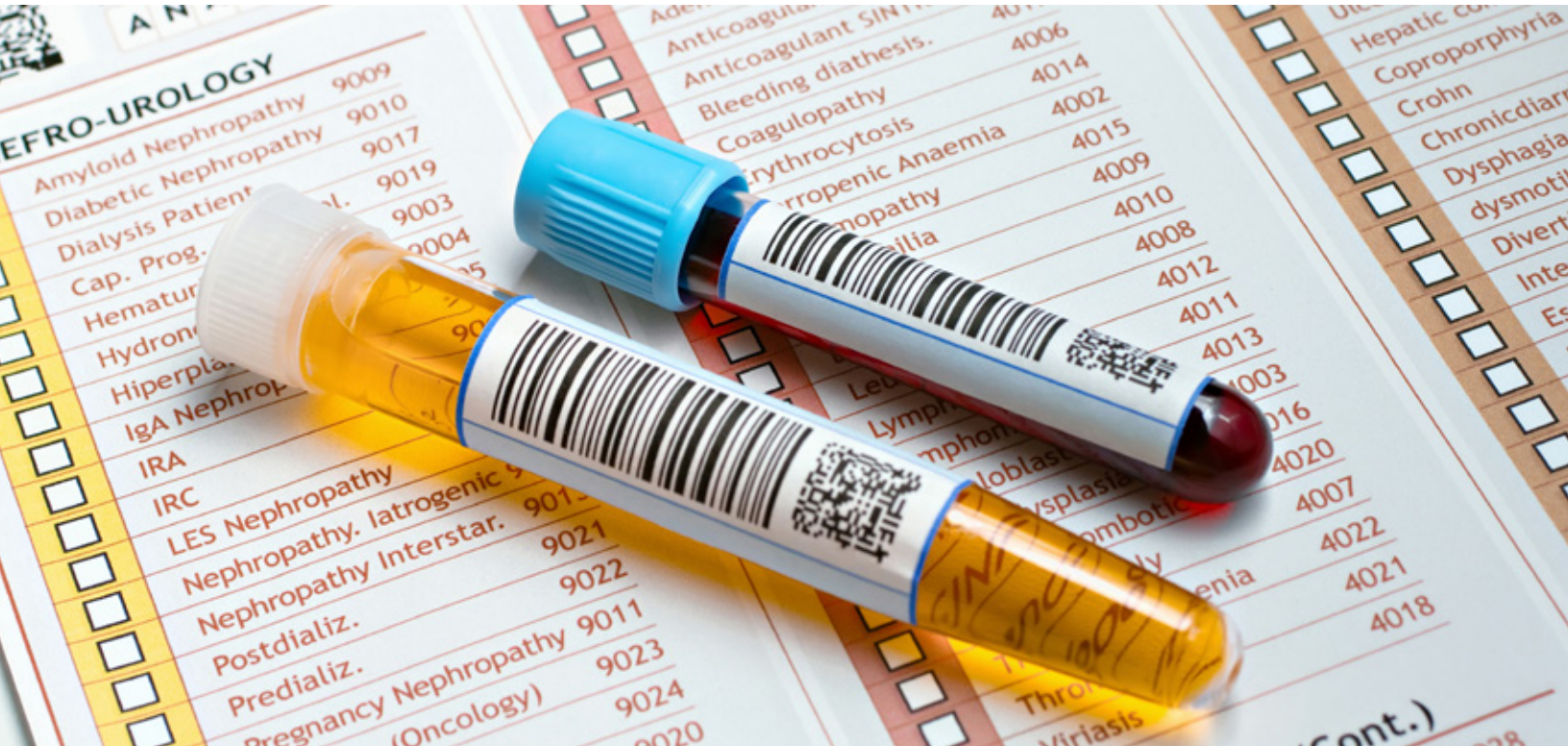
# THE CHANGING LANDSCAPE OF MEDICAL AND IN VITRO DIAGNOSTIC DEVICE REGULATIONS IN THE EUROPEAN UNION

# EXECUTIVE SUMMARY

Prompted by rapid advances in medical device technologies as well as findings of safety issues with previously approved devices, the regulation of medical devices in the European Union (EU) is undergoing a sweeping transformation. The EU's newly published regulations on medical devices include an expanded scope of regulated devices, greater oversight and control of notified bodies, greater emphasis on clinical evidence, greater transparency, and more. For most medical device manufacturers, these changes will directly impact the product review and certification process, and will increase the investment of time and resources required for product approval.

The EU's new regulations are likely to have the greatest impact on manufacturers of in vitro diagnostic medical devices. In vitro diagnostic devices, which include reagents, consumables and analyzers used in the evaluation of human specimens such as blood and urine, represent an annual global market value of approximately $50 billion (USD),[1] and are projected to exceed $22 billion (USD) in Western Europe alone by 2018.[2] Under the new in vitro diagnostic device regulation, up to 95 percent of in vitro diagnostic medical devices sold in the EU will be subject to notified body approval, up from just 20 percent currently.

This UL white paper offers an overview of the new regulations applicable to medical and in vitro diagnostic devices sold in the EU. The paper begins with a brief summary of the EU's original regulatory structure and the motivations behind the changes. The white paper then provides a summary of these changes, as well as their possible impact on device manufacturers. The paper also discusses new regulations regarding auditing and assessment activities by notified bodies, and important changes to their appointment and oversight. The paper concludes with some suggestions to effectively navigate the changing EU regulatory landscape.



## Challenges with the EU's Medical Device Regulatory Framework

For more than two decades, the framework regulating medical devices in the EU was based on three separate directives, addressing requirements for medical devices, active implantable medical devices and in vitro diagnostic medical devices.[3] Unlike the pre-market authorization scheme administered by the U.S. Food and Drug Administration (FDA) for medical devices marketed in the U.S., compliance with these "New Approach" directives has been based on conformity assessments conducted by notified bodies, independent third-party certification organizations designated by competent authorities within EU member states. Under the "New Approach," the emphasis was on the manufacturer's ability to demonstrate compliance with the relevant directives. Manufacturers whose medical devices receive notified body approval could then apply the CE mark to their products, and legally market, sell and distribute them throughout the EU.

The medical device industry is driven by scientific research and characterized by rapid and continuous technological innovation. As the global population ages and the demand for healthcare services expands, regulations covering medical and in vitro diagnostic devices must necessarily evolve to account for new technologies while continuing to protect the safety of patients. The directives formerly underlying the EU's regulatory framework for medical and diagnostic devices were originally implemented in the 1980s. Although new revisions have been periodically issued in an effort to address the introduction of new technologies, the resulting patchwork of directives, Commission Decisions and Recommendations actually made the business of compliance even more challenging for manufacturers.
Efforts to address this challenge also identified inequities in the administration of medical device regulations in individual EU member states. Directives lack the force of law throughout the EU. Instead, individual member states are responsible for passing national legislation that implements the requirements of EU directives within their respective boundaries. In addition, competent authorities in member states employed different criteria in the appointment and oversight of notified bodies. This resulted in variations in assessment rigor, potentially impacting the competitive dynamic in the marketplace and exposing patients to uneven levels of protection and safety.[4]

In addition, localized oversight of medical devices and enforcement actions against noncompliant products meant that competent authorities in EU member states could react differently to health risks identified in connection with certain devices. This issue was further exacerbated by the absence of uniform electronic registration or traceability requirements across the EU.

Concerns about the effectiveness of the EU's regulatory framework and market oversight activities were dramatically illustrated in late 2011 with the recall of breast implants produced by French manufacturer Poly Implant Prothèse (PIP). Investigators found that the company used industrial silicone in the manufacture of implants for as long at 10 years, rather than medical-grade silicon evaluated and approved during the product's conformity assessment process. At least 100,000 women in Europe and 400,000 women globally were reportedly impacted by the subsequent product recall. In France, health authorities reported in 2012 that nearly half of the 30,000 women with PIP-manufactured implants had had them removed.[5,6]

**Responding to the Challenges**

In a communication issued in 2011, the EU council noted the importance of an updated regulatory framework in supporting continued innovation in the medical device industry. "A suitable, robust, transparent and sustainable regulatory framework ... is central to fostering the development of safe, effective and innovative medical devices for the benefit of European patients and healthcare professionals," wrote the council.[7] The council called on the EU Commission to develop a "sustainable legislative framework for medical devices which ensures safety and promotes innovation."

In fact, the commission had already been considering a fundamental revision of the existing regulatory framework for medical devices prior to the council's communication in 2011. It launched a public consultation in May 2008 designed to seek the views of stakeholders, and received some 200 responses and comments. The commission launched a separate public consultation in June 2010 on technical aspects of a proposed revision to the EU's directive on in vitro diagnostic medical devices that produced more than 180 responses.

Ultimately, in September 2012, the commission released a communication outlining its plan for the restructuring of the EU's medical device regulatory framework. According to the commission, the primary goals of the restructured framework were: 1) to ensure a high level of protection of human health and safety; 2) to ensure the smooth functioning of the internal market; and 3) to provide a regulatory framework that is supportive for innovation and the competitiveness of the European medical device industry.[8]

Concurrently, the commission also published a proposed regulation for medical devices and active implantable medical devices (2012/0266)[9], and a separate proposed regulation for in vitro diagnostic medical devices (2012/2067)[10]. The proposed regulations were designed to replace the three existing directives covering medical devices, active implantable medical devices and in vitro diagnostic medical devices.

Following an extensive and complex deliberation and review process, the EU ultimately adopted two new medical device regulations in April, 2017. Regulation (EU) 2017/745[11] addresses medical devices and active implantable medical devices, and repeals EU Directives 90/385/EEC (for active implantable medical devices) and 93/42/EEC (covering medical devices). Regulation (EU) 2017/746[12] addresses in vitro diagnostic medical devices and repeals EU Directive 98/79/EC.

The new regulations provide a multi-year transition period. For medical devices, the transition period is three years, during which time a manufacturer can choose to apply the requirements of either the Directive or the medical device regulation. However, all devices must be compliant with the requirements of the regulation by the end of the transition period. An additional four years is provided to give device manufacturers time to demonstrate compliance with the regulation through the conformity assessment process. For in vitro diagnostic devices, the initial transition period is five years, followed by an additional two years for the conformity assessment process.

**Unlike directives, EU regulations have the force of law throughout the EU and are not subject to interpretation or transposition into national laws by individual EU member states.**

**Changes to EU Medical and In Vitro Diagnostic Device Regulations**

Running more than 150 pages in length, each of the EU medical device regulations consist of 10 chapters, 123 separate articles and 17 annexes. The annexes detail general safety and performance requirements, classification rules, clinical evidence requirements, and the requirements to be met by notified bodies. Some of the specific areas in the Regulations that differ from the former medical device directives include:

- *Extension of regulatory scope* - Both regulations extend the scope of medical and in vitro diagnostic devices currently regulated by the EU. Newly regulated medical devices include implants for aesthetic purposes, genetic testing products, dedicated medical software. Under the in vitro diagnostic device regulation, definitions have been clarified and the number of products requiring a notified body has dramatically increased.

- *Implementation of classification structure for in vitro devices* - In vitro diagnostic medical devices will now be subject to classification rules that allocate products to one of four risk classes. These classification rules are based on the same principles as those of the former Global Harmonization Task Force (GHTF) but are not identical to the GHTF classifications, nor to the classification structure used by either Health Canada or Australia's Therapeutic Goods Administration (TGA). Notified body approval will be required for the majority of in vitro diagnostic devices, with the exception of those that pose a low risk to patients, such as specimen receptacles.

- *Reinforced regulations covering clinical evaluations* - Expectations regarding clinical data have increased over the last decade, and the regulations place greater emphasis on the need for sufficient clinical data to demonstrate compliance with the general safety and performance requirements. With the medical device regulation, there are more stringent requirements for demonstrating equivalence, and device manufacturers are required to always consider the need for a clinical investigation. For implantable devices and those in Class III, clinical investigation is required. Demonstrating clinical safety via the equivalence route is now generally limited to those situations in which the equivalent device is a modified version of one from the same manufacturer. When a manufacturer seeks to claim equivalence with a device from another manufacturer, a contract must be in place between the parties to ensure continuous access to any relevant technical documentation.

In addition, both the medical device and in vitro diagnostic device regulations require manufacturers to provide a summary of safety and clinical performance in support of pre-market applications, that will be made publicly-available via the European Databank on Medical Devices (Eudamed). This requirement applies to Class III and implantable medical devices, and to Class C and D in vitro devices. Manufacturers must also continue to maintain post-market data for the ongoing assessment of potential safety risks. If the Regulations require specific reports to be created, they need to be compiled for both new and established devices. In the conformity assessment of some devices, e.g., Class III implantable devices and Class IIb devices used to administer or remove medicines, an expert panel may be consulted for a scientific opinion on the clinical data following the notified body assessment.

- *Implementation of unique device identification requirements* - Both regulations include requirements regarding the use of unique device identification (UDI) mechanisms to increase traceability of devices through the supply chain, and to facilitate effective product recalls in the event of safety concerns.

- *Role of "person responsible for regulatory compliance"* - Manufacturers will be required to have within their organization at least one individual responsible for all aspects of regulatory compliance. This "person responsible for regulatory compliance" must possess the experience in the field of the devices covered under the relevant regulation. Further, all economic operators associated with a given medical device have formal roles in the regulatory process, including manufacturers, authorized representatives, importers and distributors.

- *Expanded registration database of devices* - Both regulations expand the use of the Eudamed platform to provide a centralized repository of information on approved medical devices for regulators and consumers. This change is expected to increase EU-wide access to product information, thereby increasing transparency.

- *Increased regulation and oversight of notified bodies* - Notified bodies will be subject to new minimum requirements to achieve and maintain designation, and more rigorous monitoring by national authorities through witnessed audits and other mechanisms.

- *Stronger post-market vigilance and surveillance* - There is greater emphasis on post market surveillance for manufactures and notified bodies. For example, manufacturers of devices in all risk classification are required to file a periodic safety update report (PSUR). For some devices, this report is required to be filed annually through Eudamed and assessed by the notified body.

- *Greater coordination of regulatory efforts* - The regulations call for the formation of a medical device coordination group (MDCG) composed of members representing national authorities. The goal of the MDCG is to facilitate coordination between EU member states of medical device regulation and surveillance, with scientific, technical and logistical support provided by the EU Commission.

- *Other changes* - Both Regulations clarify key definitions and terms used to avoid confusion or misinterpretation. The regulations also define the legal responsibilities of medical device distributors and importers, as well as those who sell or market medical devices via the internet.

**Impact on Manufacturers**

The EU's new medical device regulations are applicable to all devices sold or marketed within the EU, regardless of where they are manufactured. For that reason, the regulations will have a number of significant impacts on manufacturers, importers and distributors of medical devices and in vitro diagnostic medical devices. These impacts include:

- *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. For example, UL estimates that nearly 80-95 percent of all in vitro diagnostic medical devices on the market will now be subject to notified body review and approval, compared with approximately 20 percent under the former framework. This means that more diagnostic devices and device manufacturers will now be regulated.

- *Increased scrutiny for high-risk devices* - The new regulations describe requirements in greater details and provide for increased scrutiny for high-risk devices. The in vitro diagnostic 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. CSs 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 and in vitro diagnostic devices that have already been authorized under the Medical Device and In Vitro Diagnostic 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 which 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.

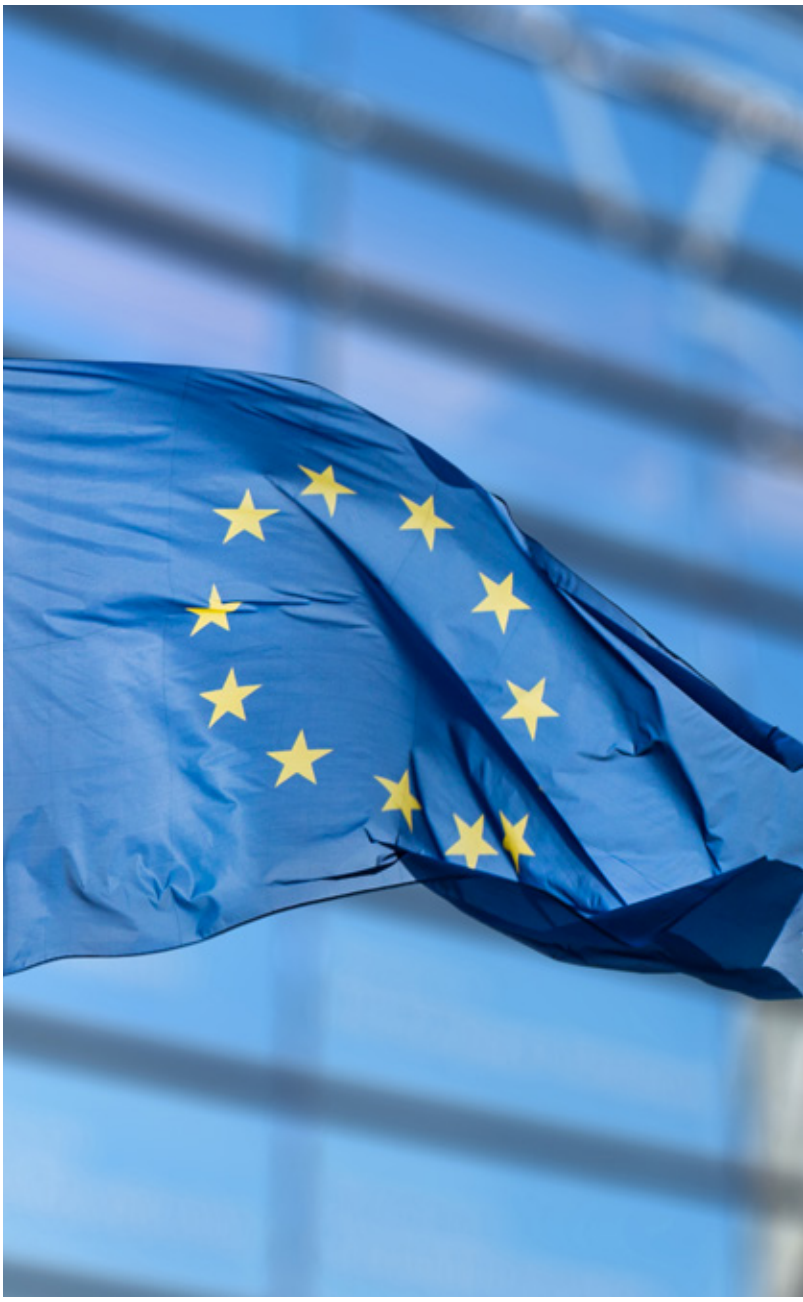
The three-year transition period for medical devices will expire in May 2020, while the five-year transition period for in vitro diagnostic medical devices will expire in May 2022. Given the investment of time and resources required to bring new medical devices to market, manufacturers are well-advised 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.

**Notified Body Issues**

All notified bodies currently designated to review medical device compliance with EU regulation are being required to reapply for designation. The EU Commission will accept applications for notified body designation beginning at the end of November 2017. Applications will be initially reviewed and assessed for completeness before an onsite audit of the notified body is scheduled. Audits are scheduled to begin in March/April 2018 and are expected to extend into at least 2019, and potentially into 2020.

Audit teams will be comprised of representatives from the commission, the national competent authority in the EU Member State where the notified body is located, and two additional competent authorities. Any corrective actions identified by the audit team will need to be addressed and receive final approval before notified body designation is granted. Due to the shorter transition period, it is expected that applicants for notified body designation under the Medical Device Regulation will be audited before IVD notified bodies.

Notified bodies are unlikely to be designated before the end of 2018 and the last notified bodies are unlikely to be designated before the end of 2019 or even into 2020. This will effectively reduce the length of the transition period for both medical devices and in vitro diagnostic devices since notified bodies will only be available for a portion of the transition period. Therefore, early and continued communication with your notified body is essential to understand when it will be designated.

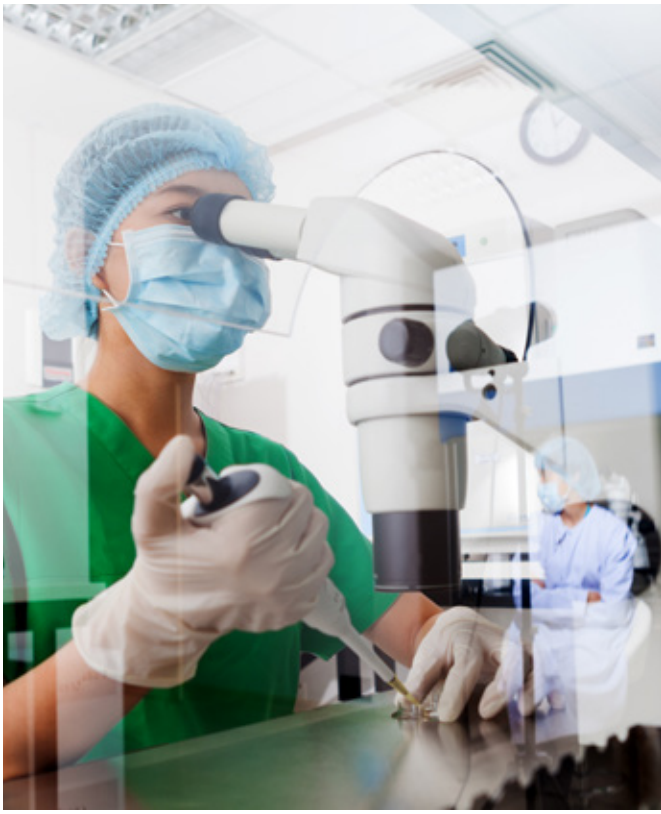


# SUMMARY + CONCLUSION

More than eight years in the making, the adoption of EU's new regulations for medical devices, active implantable medical devices and in vitro diagnostic medical devices will result in significant changes in the evaluation and approval of medical devices destined for sale or use in the EU. Manufacturers should read the regulations, identify any gaps, and start preparing now for the transition to the requirements under these new regulations to avoid delays in bringing new and innovative medical devices to market.

Device manufacturers should not underestimate the magnitude of the changes required to meet the regulations. Even fully-compliant products will require extensive and detailed reporting to conform with the requirements. Therefore, good planning as well as early communication with the selected notified body are key to help ensure continued market access throughout the EU as well as in other countries that recognize the CE mark.

For additional information about the EU's new medical device Regulations, and how UL notified body experts can support you during the transition. go to www.ul.com/medical or contact us at Medical.Inquiry@ul.com.



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