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IVDR: How to Prepare for New Regulations and Move Successfully to CE Mark

Introduction

The new In Vitro Diagnostic Regulation (IVDR) (EU) 2017/746 legislation comes into force on May 26, 2022.[1] Diagnostic device manufacturers are working hard to ensure design, manufacturing, and post-market surveillance and vigilance of their products comply with the new regulations.

As the clock ticks, few manufacturers are fully prepared: according to a survey conducted by MedTech Summit and NSF in early 2021, only 15% of respondent organizations were fully prepared to meet the IVDR deadline. One reason for the delay — COVID-19. Almost all (95%) of respondents said the pandemic had impacted their IVDR implementation.[2,12,13]

While the European Commission recently proposed to adapt the full IVDR mandatory application dates depending on the class of medical device, organizations that are not already working with a Notified Body (NB) on CE mark submission may have a tough few years ahead.

Post-market surveillance requirements is compulsory for all devices and manufacturers from May 26, 2022, onward.

Organizations that plan to transfer products from IVD Directive (IVDD) to IVDR must navigate complex regulatory requirements and guidance that often lack device-specific instructions. In addition, the IVDR may include many new products for which the previous regulation did not apply.

Note: IVDR certification of IVDD-certified devices is a new certification and not a recertification.

With a clearer understanding of the new regulations, their purpose, and a thoughtful implementation plan, organizations can move forward to bring more products into compliance with the European Regulation.

About the IVDR

The European Commission introduced *Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices* (IVDD) in 1998.[5] IVDD defined essential requirements, established harmonized standards to

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demonstrate conformity, and defined conformity assessment procedures conducted by Notified Bodies and market surveillance activities of Competent Authorities.

While the Directive worked well, an update was necessary to protect patient safety in light of advancing technology and emerging diseases. Public consultations held by the European Commission in 2008 and 2010 identified several weaknesses in the IVDD, including the lack of specific guidelines for new genetic tests and companion diagnostic devices, the demand for better alignment or harmonization with international guidelines, and an urgent need to include a risk-based classification system.[6]

What's New in IVDR?

The regulation takes a life-cycle-based approach to product compliance, starting from product design to manufacturing as well as postmarket surveillance and vigilance. The central thought behind the transition from directive to regulation is to bring about harmonization across Europe as opposed to country-specific adaptations and interpretations of guidelines. CE marking by the manufacturer (with a Notified-Body certificate if needed) allows free trade within the EU.

The IVDR and the original IVDD largely share the same basic regulatory processes. All the existing requirements under the IVDD are unchanged in the IVDR. However, the IVDR has several new specifications. To meet the objectives of its action plan, the European Commission enhanced requirements in the following areas:

- **Risk Classification System:** The IVDR uses an internationally recognized rule-based classification system for products, superseding IVDD's list-based approach. The IVDR assigns devices into one of four risk categories ranging from Class A (lowest risk) to class D (highest risk). With this new classification system, more than 80% of IVD manufacturers need oversight from the Notified Bodies. The risk classification also takes into consideration the proposed end use of the device: self-administered tests, near-patient tests used by healthcare professionals, or laboratory-use devices.

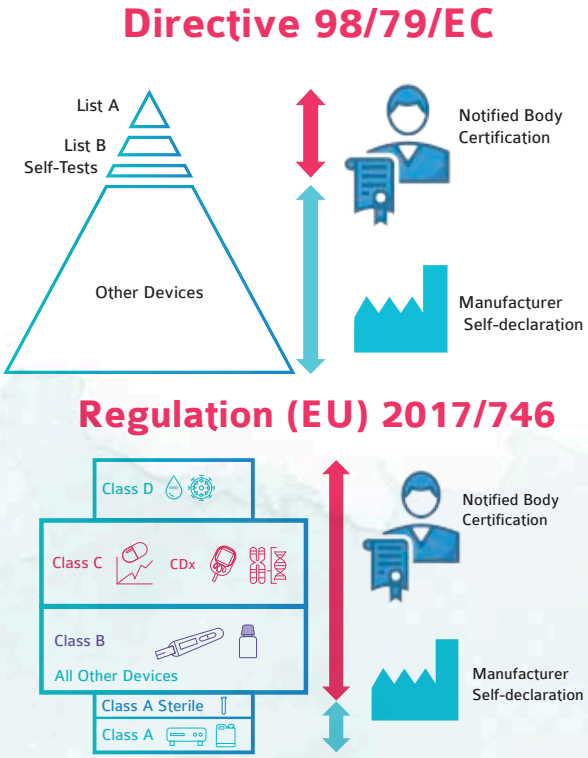

Figure 1: Description of NB involvement as a function of the list in IVDD and class in IVDR. Image courtesy of DM Experts.

CLASS	RISK LEVEL	EXAMPLES
A	*Low Individual Risk and Low Public Health Risk*	*Clinical Chemistry Analyser, General Culture Media*
B	*Moderate Individual Risk and/or Low Public Health Risk*	*Vitamin B12, Pregnancy Self-Testing, Anti-Nuclear Antibody, Urine Test Strips*
C	*High Individual Risk and/or Moderate Public Health Risk*	*Blood Glucose Self-Testing, HLA Typing, PSA Screening, Rubella*
D	*High Individual Risk and High Public Health Risk*	*HIV Blood Donor Screening, HIV Blood Diagnostic*

Figure 2: IVDR classification relies on principles recommended by the International Medical Device Regulatory Forum (IMDRF/IVD WG/N64 FINAL: 2021, formerly GHTF/SG1/N045:2008) and is based on the level of risk. Source: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-wng64.pdf

- **Oversight:** The IVDR includes more stringent requirements for the designation of Notified Bodies (NBs), with increased control and monitoring by the competent national authorities and the Commission. There are only six designated NBs currently qualified to review applications. Increased demand placed on those NBs could thus potentially delay certifications. The regulation also clarifies the obligations and additional requirements of commercial bodies (manufacturers, authorized representatives, foreign buyers, and dispensers).
- **Clinical Evidence:** The IVDR tightens requirements for clinical evidence and conformity assessment. More tests and supporting data are compulsory in order to demonstrate performance evaluations. The supporting evidence is more disease-specific as opposed to kit-based. The risks have to be reduced and monitored all along the life cycle of the device, and they must be acceptable in comparison to the clinical benefits of the device.
- **For Class D:** The conformity assessment of class D devices will require a new pre-market scrutiny step. For class D devices for which no common specifications exist and where it is also the first certification for that type of device, an independent expert panel is consulted. The EU reference laboratories shall verify the performance claimed by the manufacturer and the compliance with the common specifications, or with other solutions chosen by the manufacturer.
- **Post-market surveillance:** For each device, manufacturers must set up a post-market surveillance system proportionate to the risk class and appropriate for the type of device. Manufacturers proactively collect and review experience gained from devices they place on the market to identify any need to apply any corrective or preventive actions immediately.[1]
- **Transparency:** The IVDR enhances transparency by requiring registration and reporting information on a European database on medical devices (EUDAMED), parts of which will be publicly accessible. EUDAMED will be composed of six modules: actor registration, unique device identification (UDI) and device registration, notified bodies and certificates, clinical investigations and performance studies, vigilance, and market surveillance.[7]
- **Quality management system and technical documentation:** Manufacturers must adhere to new technical documentation requirements and ensure the implementation and maintenance of a Quality Management System (QMS).[8]

IVDR Operational and Financial Considerations

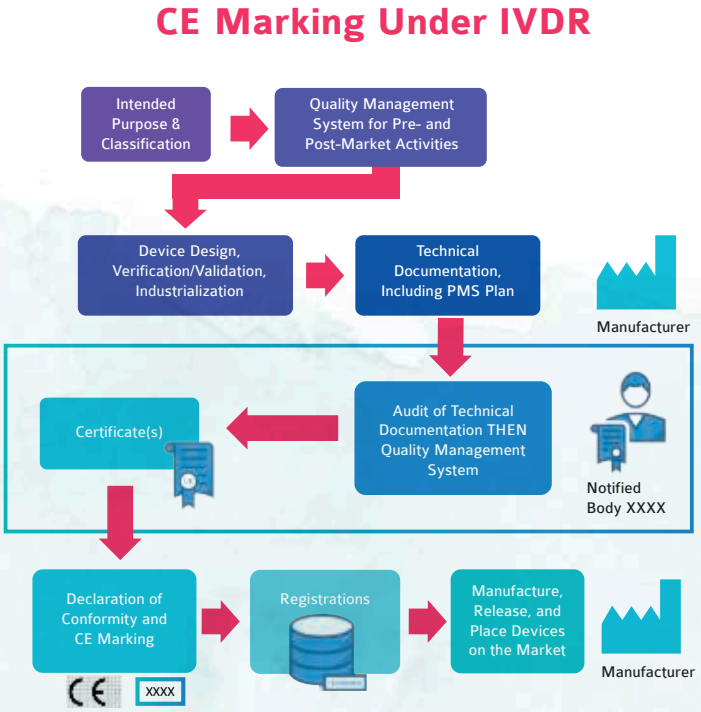

Figure 3: The process of obtaining a CE mark under IVDR requirements. Image courtesy of DM Experts.

Manufacturers will need additional resources and technology to implement the requirements of the regulation. Implementing these changes takes considerable time and expertise. They must also devote more resources toward training and/or hiring experts to navigate through the new regulations.

There are increased operational costs and time to market related to the Notified Body's involvement. Because fewer NBs are available to review diagnostics submissions, manufacturers could face delays in review periods.

IVDR Best Practices

Non-compliant IVD performance evaluation reports and documentation not only put patient safety at risk but also put manufacturers at risk of losing a CE mark. The Medical Device Coordination Group (MDCG) has provided a detailed implementation plan to help manufacturers best use their

resources and hit major milestones.

- Reviewing the Commission's step-by-step plan[11] should be the first step for any manufacturer considering getting CE approval.
- Build your documentation around the intended purpose rather than the test parameters alone.
- Consider your product's purpose and how to demonstrate clinical evidence.
- Implement risk management at all stages of product development.
- Implement a proactive post-market surveillance process.

How Manufacturers Can Comply With IVDR

The move from IVDD to IVDR is highly nuanced, and device manufacturers pay a high price for non-compliance. The notified bodies and other partners provide skilled support during this transition. Expert oversight by partnering with a third party knowledgeable in IVDR helps IVD manufacturers move toward successful registration and certification with confidence.

When evaluating a product, the notified bodies look for three types of clinical supporting evidence for IVDs: 1) scientific validity, 2) analytical performance, and 3) clinical performance.[7] Clinical performance is a reinforced type of evidence required under IVDR.

Cerba Research routinely supports IVD manufacturers from early research through to commercialization. CerbaXpert is ready to assist IVD manufacturers in their IVDR certification process. Our expertise extends from scientists of a wide range of disciplines to highly skilled laboratory technicians, regulatory specialists, and quality assurance professionals.

As part of Cerba HealthCare, Cerba Research also has access to a large global network of pathologists and a wide variety of techniques, tests, in vitro diagnostics instruments, and reagents.

Our teams work in parallel to provide:

- access to biological samples, whether remnant or ad-hoc prospectively collected samples,
- analytical and clinical performance studies,
- customized studies,
- documents required for obtaining commercialization under IVDR.

Through Cerba Xpert, Cerba Research offers IVD manufacturers CRO services for their research, device analytical validation, and their clinical affairs, all in accordance with Good Laboratory and Good Clinical Practices principles. Our team helps compile the information or authorization required for competent authorities, ethical committees, and personal data protection authorities and can act as an investigator or a sponsor.

Clinical evidence means that the information supports the scientific validity and performance for the use of a device as intended by the manufacturer.

Analytical Performance
The ability of a device to correctly detect or measure an analyte.

Scientific Validity
Validation of an analyte demonstrating an association between the analyte and a clinical condition or physiological state.

Clinical Performance
The ability of a device to yield results that correlate with a clinical condition or physiological state in accordance with the target population and intended user.

CERBA HEALTHCARE IN FIGURES

46 Nationalities
9,600+ Employees
750 Clinical pathologists
35 million patients per year
1000 Scientific publications
100 Technical platforms
750+ Laboratories
2500+ Types of tests
250,000+ test performed every day
1.3€ billon 2020 revenue

Conclusion

The IVDR aims to increase transparency, harmonize EU legislation, and bring safety regulations in line with technological and scientific advances. Implementation requires a significant change to the technical product documentation, conformity assessments, and quality management systems, all on a now-tight deadline.

However, the end result — improved patient health and safety — is a positive step forward for the diagnostics industry. To ensure compliance, partner with an expert that can help you successfully navigate IVDR and all its intricacies.

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About Cerba Research

Cerba Research, a strategic provider of diagnostic solutions, supports drug development by leveraging patient data and scientific insight to optimize R&D and commercialization globally. Providing early phase research, clinical development through central laboratory and diagnostic testing, assay and biomarker development and validation — through our global network of specialty laboratories. We partner with government agencies, non-government organizations, as well as pharma and biotech organizations to change the shape of clinical development.

Cerba Research is part of Cerba HealthCare, a leading player in medical diagnosis.

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