Decoding the New European Union In-Vitro Diagnostics (IVD) Medical Device Regulation 2017/746

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TABLE OF CONTENTS

ABSTRACT 3
INTRODUCTION 4
WHY NEW REGULATIONS ARE REQUIRED 4
WHAT IS IVDR 2017/746? 5
IVDR KEY IMPACT AREAS 7
RECLASSIFICATION 7
PERFORMANCE EVALUATION AND CLINICAL EVIDENCE 8
CONFORMITY ASSESSMENT PROCESS 8
TECHNICAL DOCUMENTATION 9
VIGILANCE AND POST MARKET SURVEILLANCE (PMS) 9
LABELING 9
UDI SYSTEM 9
MANDATORY PRODUCT LIABILITY INSURANCE 10
TRANSPARENCY 10
SUPPLY CHAIN 10
OTHER IMPORTANT CONSIDERATIONS 11
CONCLUSION 12
ABOUT TATA ELXSI 13
REFERENCES 14

ABSTRACT

The increasing growth of the in-vitro diagnostic (IVD) device global market, along with the advancements in technologies and newer innovations in the medical device space calls for stringent and unambiguous regulations to drive the industry. The equivocal nature of the current in-vitro diagnostic directive (IVDD) led to varied interpretations of the guidelines, resulting in a number of unusual and adverse events caused due to medical device malfunctioning. Such uncalled for episodes across the European Union (EU), highlighted the loopholes in the regulatory guidelines, thereby necessitating a reform to further strengthen the EU regulations.

The in-vitro device regulation (IVDR) replaces the existing three Directives 98/79/EC, bringing in a number of fundamental changes related to device classification, clinical evidence and performance evaluation, conformity assessment procedures, technical documentation, vigilance, post-market surveillance, and labeling requirements. It also introduces the Unique Device Identification (UDI) system for increased device traceability, post-market safety-related activities and reduction in errors due to malfunctioning devices in the market.

Such an enormous number of changes put considerable pressure on small and medium-sized medical device companies. They are facing many challenges pertaining to short transition timeline, lack of expertise and resources and the need to immediately change their Standard Operating Procedures (SOPs) to comply with the IVDR essential requirements, and thereby maintain market share.

INTRODUCTION

Harmonizing the national standards and decreasing regulatory barriers to facilitate trade and immediate access to new technologies is important for catering to the rising demand for in-vitro diagnostic medical devices and support the growing market globally.

The MedTech industry is witnessing a surge of innovations and technological advancements at present. With new technologies and devices replacing age-old counterparts at such a fast pace, there is an urgent need to bring in regulations that can keep up with the dynamic nature of innovations. Moreover, the increased demand for better healthcare and stringent reimbursement rules have made the medical device space a highly competitive one, with medical device companies striving to meet the rising demand for devices that provide early and accurate disease diagnosis and almost eradicate the possibilities of incorrect or delayed treatment due to underdiagnosis.

WHY NEW REGULATIONS ARE REQUIRED

In the past, there have been new regulations and amendments to the existing ones to streamline the IVD segment, such as the 1967 Clinical Laboratory Improvement Act (CLIA), that synchronized laboratories involved in interstate trade, however it did not extend to the physician office laboratories. Also, the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act incorporated IVD reagents under the definition of a device, officially bringing the regulation of diagnostics under the authority of the FDA.

Regardless of such rules and regulations, the medical device companies faced a lot of backlash due to a considerable amount of serious incidents that took place as a result of device malfunctioning. This was attributed to the various interpretations of the existing directives (IVDD, MDD, and AIMDD), highlighting the gaps in the legal system, which further led to a decline in consumer trust for the products that complied with these regulations. As a result, an alarming situation was created worldwide, prompting an urgent need for regulatory reform to strengthen the EU regulations and prevent such episodes from happening in the future.

Date	Adverse Events
August 2010	**Hip Arthroplasty Failure:** DePuy announced a voluntary recall of its ASR metal-on-metal hip replacement system after the analysis of five year study report which showed the product failure rate was about 1.3%
July 2011	**Surgical Mesh Complication:** The United States Food and Drug Administration (US FDA) warned of serious problems associated with surgical mesh for trans-vaginal repair after nearly 4000 adverse events
June 2012	**Breast Implant Crisis:** Poly Implant Prothèse (PIP), a French company, was revealed to have knowingly sold breast implants made with industrial-grade silicone, rather than medical-grade, resulting in about 300000 women being affected
July 2012	Whistle blowers claimed that the FDA had approved medical devices that posed severe health risks

Table 1: Account of adverse events/incidents

WHAT IS IVDR 2017/746?

The new EU IVDR aims to address the weaknesses of the IVDD, ensure quality, safety, and reliability of devices, thereby allowing smooth functioning of the IVD market. The regulations are designed taking into account small and medium-sized enterprises that are active in this sector.

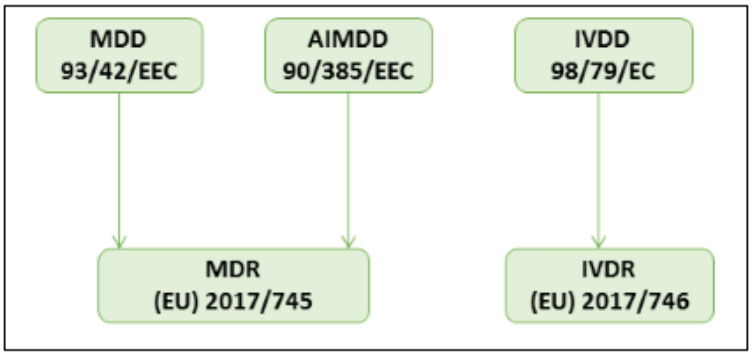

Figure 1: Regulatory reforms

After years of intent considerations and dialogs with major stakeholders, a comprehensive regulation document was published by the European Commission in 2012, replacing the existing directives.

2008	EU Commission: consultation on medical device framework
2012	EU Commission publishes a proposal for new MD Regulations
2014 Q2	EU Parliament: position on MDR and IVDR
2015 Q3	EU Council adopts position on proposed Regulation
2015 Q4	Trilogue: Commission, Parliament, Council
5th April 2017	2 New Regulations on medical devices were adopted (MDR and IVDR)
25th May 2017	New Regulations entered into force (MDR and IVDR)

Table 2: Timeline for regulation reforms

As per EU Commission, there was a need to initiate migration from Directives to Regulations, to ensure a broader scope of safety and more effective implementation of the rules on medical devices and in-vitro diagnostic medical devices. These new regulations replace the existing directives[3].

- Regulation (EU) 2017/746 of the European Parliament and the Council of 5-April-2017 on in-vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
- IVDR will replace the EU's current In Vitro Diagnostic Device Directive (98/79/EC) with a five-year transitional period.

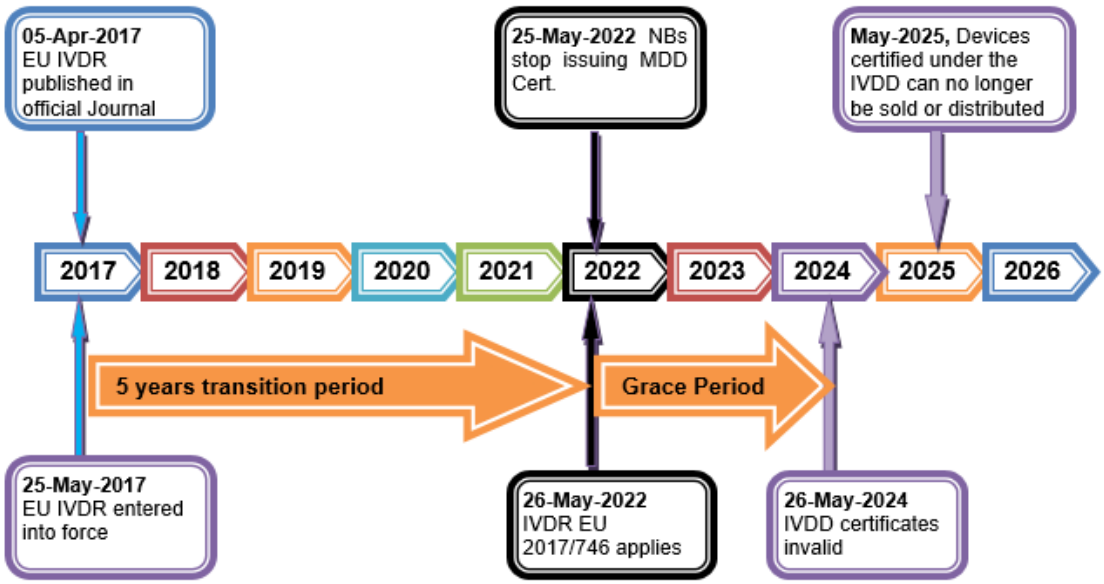

Figure 2: IVDR transition timeline

	IVDD 98/79/EC	IVDR (EU) 2017/746
Legislative Framework	Directive: Requires transposition in each member state	Regulation: Immediately applicable and enforceable by law in all member states
Pages	37	157
Articles	24	113
Annexes	10	15
Notified body (NB)	80-90% of the products do not require NB intervention	80-90% of the products requires NB intervention

Table 3: The EU Official Journal publication differentiation: IVDD vs. IVDR

IVDR KEY IMPACT AREAS

The new IVDR provides a more significant structure and control for IVD medical devices**.** Below are the key impact areas of IVDR[3,4,5,6].

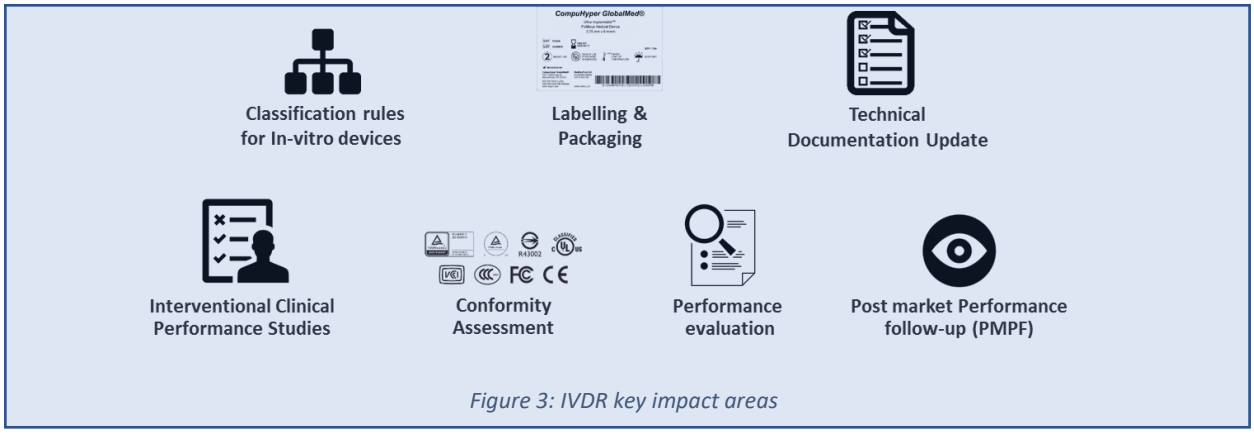

Figure 3: IVDR key impact areas

Reclassification

IVDR 2017/746 introduces seven classification rules and four risk-based classes, with 'Class A' representing the lowest risk and 'Class D' the highest risk. Annex VIII, Classification Rules of the IVDR lays down the groundwork for changes affecting new regulatory pathways for IVDs.

IVDR compliance requires self-declaration of products by the manufacturer to more stringently controlled risk classes, and mandates Notified Body (NB) intervention. While 'Class A' IVDs will not require NB involvement, it is the manufacturers' responsibility to declare conformity with the regulation. Furthermore, 'Class A' sterile IVDs, 'Class B', 'Class C' and 'Class D' IVDs require will require NB assessment. Within a five-year transition period, at least 80% of IVDs will require CE marking for lawful distribution within the EU common market.

Impact

IVD medical devices manufacturers are required to carefully examine the IVDR classification rules in Annex VIII to conclude whether new conformity assessment rules are now applicable to their product portfolio. If so, they need to be in touch with the NB (where necessary) and take steps to evaluate the required timescales involved in implementing this change.

Under the existing directive, the majority of IVDs (approx. 80%) on the EU market are self-declarable and do not have NB oversight, however, under the IVDR; this proportion will change inversely.

In Vitro Diagnostic Device Class	Examples
Class D: High public health risk, high personal risk (Rule 1)	• Devices intended to determine any of the following markers: • ABO system • Rhesus system • HIV 1/2 • Hepatitis C/B virus
Class C: High personal risk, moderate to low public health risk (Rules 2,3,4)	• Devices used for blood grouping or tissue typing • To be used in screening, diagnosis, or staging of cancer • For human genetic testing

Class B: Moderate to low personal risk, low public health risk (Rules 4,6,7)	• Devices • for the detection pregnancy • for fertility testing • for determining cholesterol level • for evaluating thyroid function
Class A: Low personal risk, low public health risk (Rule 5)	• Products for general laboratory use, • Accessories, wash buffers, specimen receptacles, instruments and culture media

Table 4: IVD device classification

Performance Evaluation and Clinical Evidence

A detailed explanation of the performance evaluation plan and the results of the clinical performance studies as part of the Performance Evaluation Report (PER), makes up for a highly important aspect of the entire technical documentation for CE compliance.

Additionally, interventional performance studies may be required for the higher risk classes of IVD devices (Class C and Class D)

The IVDR requires clinical evidence and post-market performance follow-up, thus providing a lifecycle approach. This necessitates a performance evaluation plan and report, that describes how to demonstrate scientific validity, analytic performance, and clinical performance.

For high-risk devices, class C and class D manufacturers must update the safety and performance aspects together with performance evaluation annually and make this publicly available. Performance evaluation reports are also required for Class A and B IVD devices, but need not be updated annually.

Impact

IVDR requirement is to obtain additional clinical evidence. For class C and D high-risk devices, performance evaluation report scrutiny will be done by NBs and reports must be made publicly available.

Conformity Assessment Process

Each manufacturer should conduct a performance evaluation, establish and maintain a risk management system, along with current and up-to-date documentation of sufficient quality to allow assessment of the product conformity with the regulatory requirements following post-market approval.

Class C and D IVD products can alternatively get CE marking following a conformity assessment of the product type, technical documentation, and production quality.

Impact

Each manufacturer must have a performance evaluation plan and proactive Post-Market Performance Follow-up (PMPF) plan to include a post-market surveillance plan.

Technical Documentation

The IVDR is significantly more prescriptive about the compelling content of technical documentation (IVDR Annex II and Annex III)

Essential Requirements (ERs), as initially defined in IVDD, are now referred to as 'General Safety and Performance Requirements' (IVDR Annex I) with the expansion in the number of requirements.

Impact

The required technical file/design dossier documentation is genuinely based on the current Global Harmonization Task Force (GHTF) and Summary Technical Documentation (STED) guidance document reflecting the harmonization intent of global regulators.

Technical File sufficiency, including associated checklists, must be checked in detail.

Vigilance and Post Market Surveillance (PMS)

Under the new Regulation 2017/746, manufacturers need to collect post-market clinical data as part of their ongoing evaluation of potential safety risks.

Manufacturers can report serious incidents, field safety notices, and periodic summary reports to competent national authorities through an electronic database called EUDAMED.

Serious incidents reporting timeframes are tightened from 30 days to 15 days (IVDR Article 82). There will be new electronic vigilance reporting (IVDR Article 87) and Periodic Safety Update Reports (PSUR) for all IVDs (IVDR Article 81), subject to the different frequency and submission requirements.

Impact

Each manufacturer is required to have a Post-Market Performance Follow-up (PMPF) plan to include a post-market surveillance plan and vigilance activity plan. This requires an additional resource in functions that supports products on the market, such as Regulatory and Medical Affairs.

Labeling

Under IVDR, the requirements for product labeling are more prescriptive than before.

Information on residual risks shall be included as limitations, contraindications, precautions, or warnings. Information supplied by the manufacturer should be up-to-date and made available on the manufacturer's website (IVDR Annex I Chapter III).

Impact

Manufacturers must review the sufficiency of their product labeling and availability on their websites.

UDI System

The requirement of the Unique Device Identification system (UDI System) to trace all IVDs placed on the EU market (except custom-made devices). UDI system significantly improves the effectiveness of post-

market safety-related activities for devices. For each IVD device there will be an assigned UDI obtained from a UDI supplier, and this information must be uploaded into EUDAMED.

Impact

Manufacturers must plan for UDI implementation.

Mandatory Product Liability Insurance

Manufacturers need to provide adequate financial coverage for their potential liability. This provision will be based on risk class, type of device, and the size of the enterprise (IVDR Article 10.15).

Impact

There is a need to revise the Product Liability provisions by the manufacturers to assure their ownership in the right direction.

Transparency

Transparency, as per definition refers to, "transparency in and sufficient access to information, suitably accessible for the user, are important in the interest of the user, to protect user's health, to offer a sound base for regulatory decision-making and to build confidence in the regulatory system."

The European Data Bank on Medical Devices (EUDAMED) (IVDR Article 33) will be made public for specific devices, where the manufacturers need to report all of their products into the EUDAMED database.

Impact

Manufacturers are required to continuously and closely monitor the EUDAMED system and organize for its implementation, to be able to ensure smooth notification of all products to the EUDAMED database.

Supply Chain

Each manufacturer is required to appoint a 'Qualified Person' responsible for Regulatory Compliance (PRRC). IVDR Articles 11 & 28 states that "the authorized representative should be jointly and severally responsible with the importer and the manufacturer."

Distributors and Importers (Economic Operators in the supply chain) are now explicitly regulated (IVDR Articles 16 and 22) and have specific regulatory obligations as well.

Impact

Manufacturers must consider the entire supply chain to ensure that these requirements are adequately addressed and agreed with their business partners.

Other important considerations

Transition timeline

The IVDR is associated with a five-year transition period following its publication and thus, in 2022 enter fully into force. After this date, IVD devices with a CE mark issued against the Directive 98/79/EC will become void.

Notified Body unannounced inspection

Under the new IVDR, Notified Bodies are required to conduct unannounced inspections of manufacturers, hence medical device companies need to stay up-to-date with their documentation for a possible audit.

Expertise

The IVDR requirements necessitate qualified and accredited individuals. In case, experienced researchers/technical writers are not available in-house, manufacturers are required to develop or procure appropriate expertise.

Adequate Resourcing

Many companies are finding it difficult to manage the increased workload triggered by the new regulation with the internally available resources alone. To cater to this, medical device companies are engaging with service providers in order to achieve compliance within the designated timelines and existing resources.

CONCLUSION

The In-Vitro medical device space is set to witness a sea change with the advent of new and more stringent regulations. The great number of amendments to the previous directives, require medical device companies to carry out major transition activities in crunched timelines. The manufacturers are expected to chalk out the best possible approach and achieve the targeted remediation goal in a limited number of attempts, given to the reduced number of notified bodies. Moreover, the high volume of work and unpredictability is adding to the pressure faced by the companies.

Manufacturers are looking out to retain their products in the market and gather additional market share by smoothly transitioning their products as per the new regulations. However, the haze around the new requirements, the lack of expertise to accurately comprehend and execute such intricate processes without adequate project management controls are major roadblocks.

Manufacturers must have a proactive approach in planning and working out a flawless project execution methodology that fits their needs, taking into account the gaps that need to be filled across the product portfolio, greater clinical and performance evidence requirements, increased transparency and device traceability and the required effort to implement enormous amount of changes in time, while containing the cost of compliance.

ABOUT TATA ELXSI

Tata Elxsi is a design company that blends technology, creativity, and engineering to help customers transform ideas into world-class products and solutions. Tata Elxsi has extensive experience in helping companies launch medical imaging, in-vitro diagnostic, patient monitoring, therapeutic and surgical devices in developed and emerging markets.

Tata Elxsi has been instrumental in helping global companies transition from MDD, AIMDD, and IVDD to EU MDR and IVDR. Two years into transition, Tata Elxsi's custom agile-based project management for the healthcare industry is benefiting medical device manufacturers to handle high volume implementation and unpredictability associated with the transition.

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