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# THE NEW IN-VITRO DIAGNOSTIC REGULATION (2017/746/EU): CHALLENGE OR AN OPPORTUNITY FOR MANUFACTURERS AND KEYSTAKEHOLDERS

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## ABSTRACT

**Background:** The European Union (EU) market is burgeoning with about 500,000 kinds of competitive and novel medical and In vitro diagnostic devices (IVD), with mushrooming of small and medium-sized enterprises (SME). Since 1990, on the concept of New Approach, it was regulated by the legal framework of 3 main directives, Directive 90/385/EEC on AIMDD, MedicalDevice Directive 93/42/EEC (MDD) and Directive 98/79/EC (October 1998 ) on IVDD. With the incident of metal on metal hip prostheses (Aug 2010), transvaginal mesh complications (July 2011), and Breast implant crises (June 2012), the need for a revision process started in 2012. In May 2017, the two new regulations were published in; Regulation (EU) 2017/745 replacingdirective on AIMDD and MDD and Regulation (EU) 2017/746 (IVDR) replacing IVDD. **Methods:** European Union Directives and published articles were reviewed. This study helps to understand that how it affected patient safety, and impacting the SMEs, regulatory authorities, research and health care industry. **Discussion:** With the new rule-based risk classification, the NB oversight has been increased from 7 to 84%, and due to lack of approved EU reference lab and official guidance documents, maybe 22% of the test currently placed on the market will be lost to the transition. For the manufacturers, these changes resulted in recruiting more skilled resources, time-consuming processes and thereby translated to an increase in the cost of the final product. This leads to prioritization of their portfolio and will have a direct impact on the sector of innovation research, resulting in mergers and acquisitions of SME by big

companies. On the other hand, due to the new stringent regulations, will trigger the introduction of smart, efficient, and environment-friendly technologies. There will be an increase in the scope of medical and regulatory affairs roles and the new regulation will ensure patient safety, device efficacy and product transparency.

**KEYWORDS:** In-vitro Diagnostic (IVD), In-vitro Diagnostic Directive (IVDD), In-vitro Diagnostic Regulations (IVDR), active implantable medical devices directive (AIMDD), Directives, Notified Body (NB), EU, small and medium-sized enterprises (SME).

## INTRODUCTION

### Evolution of IVDR[1]

The EU's legal framework defines the requirements to assure the highest degree of public well- being, quality, safety and effectiveness of approved medicines. It is predicated on the idea that one must first get marketing authorization from competent authorities, before releasing a pharmaceutical product on the market. The need to avoid a repeat of the thalidomide catastrophe In the late 1950s, in which thousands of infants were delivered with limb abnormalities due to their mothers using a pharmaceutical medication during gestation, was a major driving force behind the creation of the legislative framework. After that, a vast body of law has sprung up under this concept, with the gradual harmonization of standards for marketing authorization, and post- marketing surveillance, applied throughout the entire European Economic Area (EEA).[2]

The first EU law (Council Directive 65/65) on human medicines was published in 26 January 1965 on the idea of the law relating to medicinal products.[3] Council Resolution 1985, was the first attempt to describe the new approach. This stipulated that any new approach to regulation would be confined to identifying the key essential requirements for a wide range of items, with precise technical specifications outlined in harmonized European standards.[4] In 1989, a Council Resolution on the Global Approach further developed the new approach. The CE mark was formed as a result of this, which manufacturers could affix to their offerings, provided they have proven compliance with the essential requirements.[5]

In 1990 on new approach (first attempt in 1985 and further revised in 1989), the EU harmonized standards on the effectiveness and reliability of medical devices with three basic legal frameworks; Council Directive 90/385/EEC of 20 June 1990 on active implantable medical devices, followed by Council Directive 93/42/EEC of 14 June 1993 appertaining to

medical devices and Directive 98/79/EC of 1998 on in vitro diagnostic medical devices (IVDD). Their objective was to assure the hindrance free operation of the European market as well as a highest standards of human health and safety protection. Six amending or applying Directives, along with the most recent technical reformcarried on by Directive 2007/47/EC, have been added to them throughout the period.

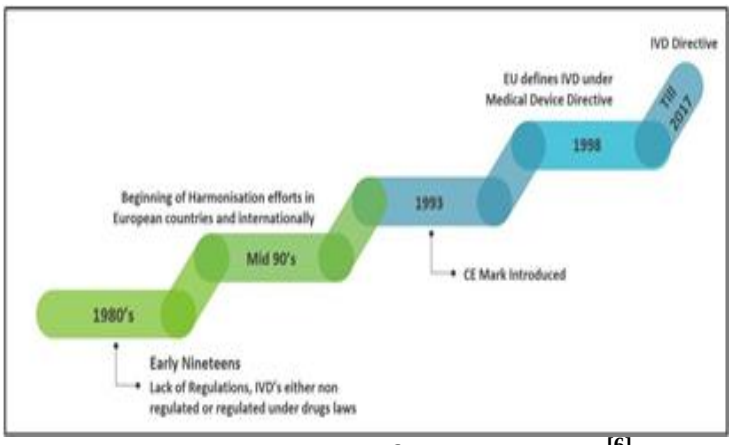


**Figure 1: Evolution of IVD Directive.**[6]

The Key highlights of IVDD (Directive 98/79/EC) are to list Essential Requirements that the manufacturer has to demonstrate before placing into the market, the Establishment of risk management, and systematic Medical event reporting (Vigilance), and the introduction of common Technical specifications for high-risk products. In IVDD the high-risk product undergoes strict assessment, by a third party called a Notified Body. These NB's are independent organizations, accredited by an authorized accrediting body designated by the Member state. The European Commission maintains the database of accredited NB's - The Nando information system2.

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 devices malfunctioning.[7] In August 2010, DePuy ASR™ metal-on-metal hip implants were recalled due to the occurrence of the metallosis in the bloodstream. These failures show a flaw in the clinical evaluation and post- market surveillance requirements.[8] In July 2011, Surgery mesh for transvaginal repair has significant side effects that the US FDA has warned about. In June 2012, about 300,000 women were compromised by the sale of Poly Implant Prosthese breast implants, made with industrial- grade silicone instead of medical-grade. The counterfeit manufacturing of PIP silicone breast implants exposes the deficiencies in the legal framework that have undermined the trust of EU patients and healthcare providers.

This originated from a lack of cooperation between Notified Bodies (NBs) and Competent Authorities, which was caused by different interpretations of the existing directives (IVDD, MDD, and AIMDD), resulting in the application of directives differently across Europe and thereby highlighting the gaps in the legal system. There were varying degrees of competency associated with NBs that missed the skills and knowledge to properly assess the clinical evidence, relevant risk vs benefit ratio, patient safety, lack of openness and accessibility to data for patients, healthcare providers, and producers.

Due to these episodes, an alarming scenario has arisen throughout the world, necessitating an immediate regulatory change to reinforce EU legislation and avoid repeat occurrences in the future. In 2012, the EU Commission recommended updating the existing regulatory framework by replacing the MDD and IVDMD with the Medical Device Regulation (MDR) and the IVDR. The EU parliament reacted in 2014 with a set of revisions to the recommended regulations and the EU Council provided its informal opinion on the recommendations in 2015. In June 2016, the agreed-upon articles were published. The regulations were translated into the official EU languages and subjected to any appropriate statutory checks before being officially accepted by the EU Parliament in April 2017.

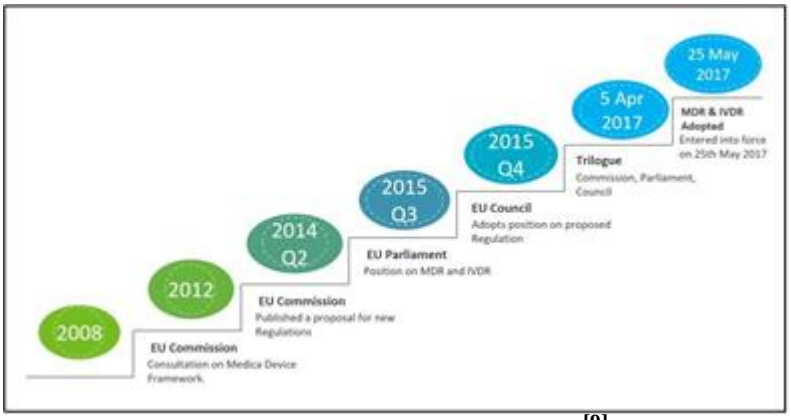


**Figure 2: Evolution of IVDR.[9]**

After being published in the Official Journal of the EU, Regulation (EU) 2017/746 on IVD, became effective in May 2017. With a five-year transitional phase, the new regulation, known as the European In Vitro Diagnostic Medical Device Regulation (EU IVDR), will revoke and supersede the EU's existing IVDD (98/79/EC).[10] According to the Article 110 on Transitional Provisions "Certificates granted by Notified Bodies in conformity with IVDD from 25 May 2017, must be void by 27 May 2024. IVDs who got certificates in compliance with IVDD before 25 May 2017, are still acceptable till the period mentioned on the

certificate, baring those issued under annex VI of IVDD, shall be valid till 27 May 2024. The IVD can be on the market or put into operation until May 27, 2025, if it is legitimately placed on the market under IVDD before 26 May 2022, and put on the market by a certificate from 26 May 2022.[11]

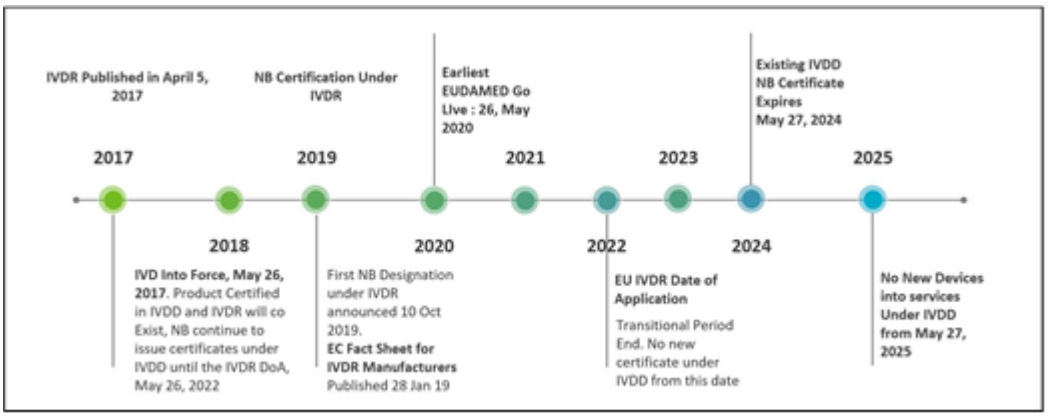


**Figure 3: IVDR 2017/746 Transition Timelines (Wolf M 2018).**

## MATERIALS AND METHODS

The proposed study was done on the IVD medical device keeping in mind the key changes, that has taken place with the implementation of the new EU IVDR, from 26$^{th}$ May 2022, but due to the COVID-19 outbreak, EU has extended the date of application to May 2025 for Class D Device, May 2026 for Class C Device and May 2027 for Claas B and A sterile device.[12]

The critical study of IVD medical devices regulations was done based on:

a) IVDR 2017/746.[13]
b) Recast of the medical device directives.[14]
c) IVDD 98/79/EC.[15]
d) MedTech Europe Survey Report.[16]
e) Essential Principles applicable to Medical Device.[17]

### Key changes in EU IVDR

As the diagnostic industry witness transformational changes by the enforcement of IVDR, there is a time challenging task for economic operators, notified bodies, and regulatory consultants to carry out the transition.

**Definition and Scope:** Under IVDR, definition of an IVD has been expanded and clearly stated to include tests meant to detect a medical condition or a disease, companion

diagnostics, and software (Article 2). Additionally, it adds a few more definitions and raises the number from 10 to 74.

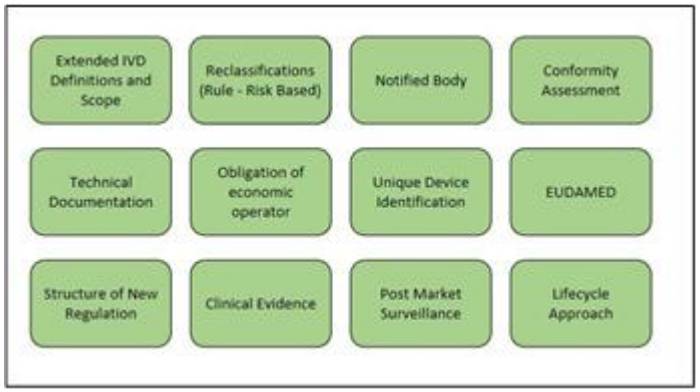


**Figure 4: Key Changes in IVDR.**

**Reclassification:**[18] The new rule-based risk classification method is highly adaptable as compared to list-based method it succeeds, enabling the IVDR to catch up with the development of technology and the necessity to treat newer health issues. The manufacturer shall refer to the guidelines stated in Annex VIII of the Regulation while classifying their equipment. There are 10 implementing and 7 classification rules, resulting in four risk-based classes. If multiple rules are applicable, the rule with the greatest classification must be applied. In accordance with the new IVDR, devices should be categorised into classes A, B, C, and D based on their intended use and associated risks, in line with international practices.

**Notified body:**[19] IVDR brings assessment, designation and supervision of NBs by the Member States, based upon precise as well as stringent standards, will therefore be subjected to command at the Union level. The authority responsible for NBs, shall carefully examine NB's evaluation of manufacturer's technical documentation, especially report on performance evaluation. In case of class D devices, competent authorities must be notified on the certification issued by NBs and provided the authority to examine the evaluation performed by NBs.

**Structure of new regulation:** In contrast to the IVDD 98/79/EC, which was designed with articles and annexes, the IVDR 2017/746 is arranged into chapters, sections, articles, and annexes. It has 113 article numbers across 10 chapters, 15 annexes and 157 pages. This is a significant reform that will dramatically improve the rigor and strength of laws regulating goods entry into EU markets.

| | IVDD 98/79/EC | IVDR (EU) 2017/746 |
|---|---|---|
| Legislative Frame work | Directive : Require Transportation in each menber state | Regulation : Immediately applicable and enforcement by law in each member state |
| Pages | 37 | 157 |
| Articles | 24 | 113 |
| Annexes | 10 | 15 |
| Notified Body (NB) | 80% of the products do not require NB intervention | 80% of the products requires NB intervention |

**Figure 5: Structural difference between IVDD and IVDR.**

**Conformity procedure:** As since the class A devices offer minimal risk to user, the conformity evaluation process for these devices shall by general law, be carried out only by the manufacturers. For class B, class C and class D devices, an adequate degree of engagement of an NB, with an approach for the evaluation of technical documentation, must be mandatory. Article 10(8) requires the manufacturer to create, record, and execute a quality management system (QMS) and ensure that it remains effective throughout the device life cycle.

**Technical documentation:** With the increase in the number of criteria, Essential Requirements (ERs) have been renamed 'General Safety and Performance Requirements' (IVDR Annex I). The manufacturer's technical documentation on post-market surveillance, which must be prepared in compliance with Articles 78 to 81, must be provided in a concise, organized, easily accessible, and understandable manner, and must encompass, in addition, the items listed in Annex III. Every year, producers of class C and D devices are required to prepare and maintain a periodic safety update report ('PSUR') for every device.

**Obligations of economic operators:**[20] This regulation clearly defines the obligations of the manufacturer, importer, distributor, and authorized person. The following articles contain detailed explanations of these changes: 10, 11, 13, 14, and 30. Article 10 requires manufacturers to establish risk management (paragraph 2) and quality management (paragraph 8) systems in place, as well as to conduct performance evaluations (paragraph 3), create and maintain technical documentation (paragraph 4), and follow a conformity assessment procedure (paragraph 5). Producers are indeed accountable for its products once they hit the marketplace, and must take necessary remedial steps, document and notify incidents, and provide authorities with acceptable evidence of conformity (paragraphs 11, 12, 13). Manufacturers should set up the mechanisms to address their economic obligation, due to the injuries occurred by faulty equipment (paragraph 15). As per Article 15 mentioned in

IVDR, a dedicated person must be assigned by each manufacturer for regulatory compliance.

**Unique Device Identification system (UDI):** The adoption of a UDI system intends to boost the tracking of all medical devices available by providing a unique code on the device's label. UDI has several benefits and will mostly be used to record significant incidents and identify counterfeit medical devices. The details of this new method are clearly outlined in Articles 24 and 87.

**Eudamed:**[21] With the new regulation, the Eudamed database would then keep information about post-market surveillance programs, safety and clinical performance studies, PSUR, also provide further detailed information on clinical study data, manufacturers, Unique Device Identification Information (UDI), single registration number and device registrations. Article 33 of the official publication contains extensive information on the Eudamed amendments.

**Clinical evidence:**[22] One of the important inclusion in IVDR is the, proof of compliance with the general safety and performance requirements must be supported on clinical evidence, that is scientific validity, the analytical performance and clinical performance of the device. It is essential to make sure that the clinical evidence of devices is maintained across the product lifecycle and must define the intended use of the equipment as mentioned by the producer.

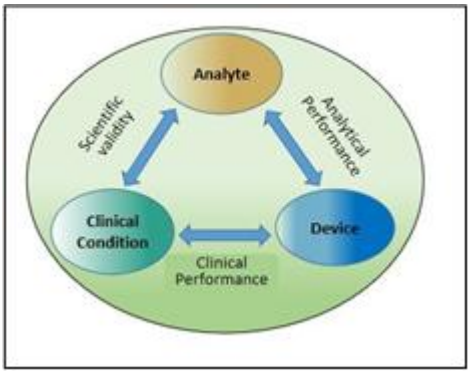


**Figure 6: Understanding of clinical evidence.**

## RESULTS AND DISCUSSION

### Impact on key stakeholders and manufacturers

**A Paradigm shift in Notified Body oversight due to new Rule Risk Classification**:[23] Class A' IVDs need not require NB involvement under the EU IVDR 2017/746, and manufacturers will be responsible for declaring conformity with the regulation. Moreover, 'Class A'sterile IVDs, 'Class B', 'Class C' and 'Class D' IVDs require will require NB

oversight.[24] Hence, most of the IVDs in the EU Market (approx. 80%) on the EU market are self-declarable and do not have an assessment by NB, however, under the IVDR; this percentage will shift conversely.[25] According to MedTech's most recent survey, even this is underestimated: the actual ratio is 92:8 under the IVDD and 22:78 in the new IVDR.

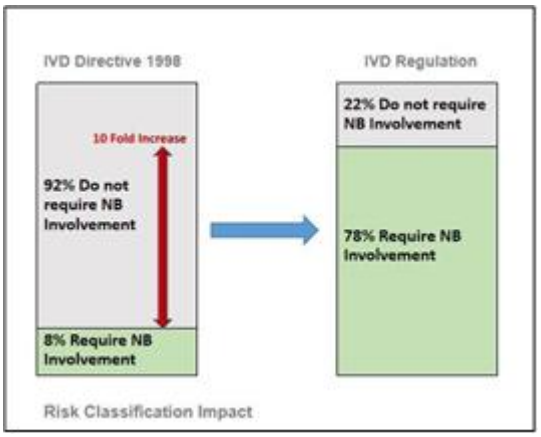


**Figure 7: Impact of Risk classification on Notified Bodies.**

**The increasing workload on notified bodies**:[26] Given that 34,000 of the 40,000 existing IVDs will require re-certification by a notified body[27,28] MedTech Europe hypothesized that "if all IVDD notified bodies cleared for IVDR designation, and thereby each would on average need to assess at least 1,600 IVDs, against their normal capacity to certify 205 devices a year at max, which means an increase in the workload of 780 percent or almost by factor of 8. This seems to be unrealistic in the real world.

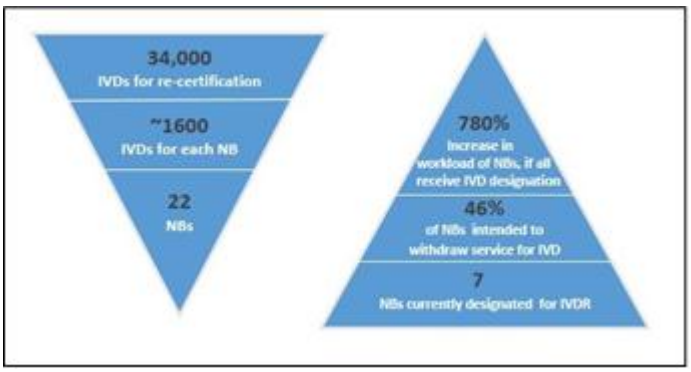


**Figure 8: Impact on the workload of NBs with the IVDR**

**Grave shortage of notified bodies:**[29] Out of 18 designated notified bodies in IVDD, so far only 7 have been designated to the IVDR.[30] As a result,[31] enterprises may struggle to timely connect with a NB or else cease to function in the conformity assessment procedure, and so may not be able to have all of their IVDs approved prior to the IVDR's full implementation.[32] Adding fuel to the fire, approximately half of the notified bodies surveyed

(46%) said they had no intentions to apply for designation in the EU IVDR. According to Lakshman and Ciara; expert committees and approved reference labs, which are required for high-Risk device assessments are falling short, the EUDAMED database is behind schedule; and many crucial guidance documents for understanding and execution of the requirements are still pending. As a result, the surveys provided information on the predicted shortage of IVDR-designated NBs.

**Tests lost in the transition:**[33] Manufacturers are anticipating migration of up to 31118 IVDs under the new rule, compared to 39844 under the IVDD Directive. This would result in a 22 percent reduction in the number of IVDs accessible to health care providers for patient treatment. Small and medium-sized firms will experience the greatest percentage loss of IVDs.

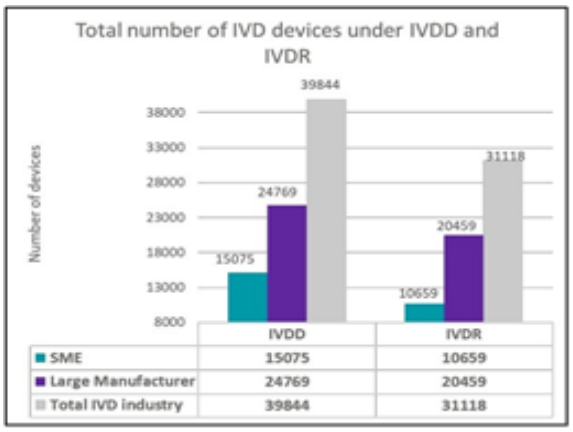


**Figure 9: Some IVDs will be unavoidably lost in market the.**[34]

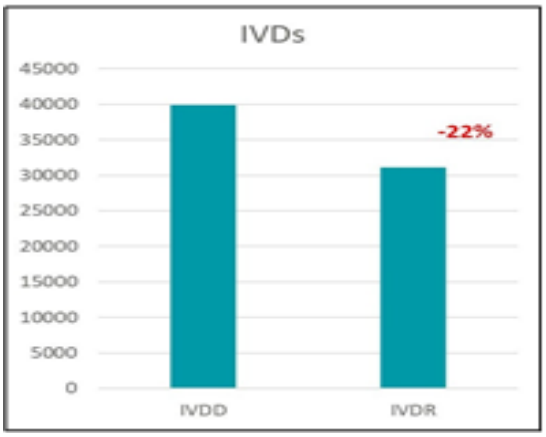


**Figure 10: SMEs will lose a greater proportion of their transition to IVDR**

**Prioritization of the portfolio:**[35] The aforementioned effects will cause SME's to consider if it works better to streamline their portfolio or make changes to their product offerings. Is it part of your goal to look into non-EU markets and collaborate with companies outside of the IVD medical device industry? Is your present revenue model assisting you in carrying out your transition strategy? Is the C-suite, including the CFO and COO, properly involved, and is there a committed team in place to execute the strategy? Have you mapped reclassified items to NB criteria and found relevant NBs? Have you contacted NBs to find out whether they've filed for IVDR designation?

Manufacturers may have to choose their portfolio; for instance, their highly significant and lucrative items may be applied for CE certification, whereas other goods may become

temporarily closed or may be abandoned. "This triggers manufacturers to assess, whether to continue in this domain and if yes, then what is the probability of success. Accordingly, they need to revise their procedures and product portfolios in the light of current advancements, ensuring that they continue to assist patients and stay ahead of the competition. According to Shayesteh Fürst-Ladani, founder and CEO of SFL (Solutions for Life Sciences) in Basel, "several enterprises have already begun to assess the manufacturer's product offering."

**Merger and acquisition by the big companies:**[36] Serge Bernasconi, CEO of MedTech Europe, agrees. "With the implementation of IVDR, nearly eighty percent of IVDs will now undergo CE certification from a Notified Body. Companies might decide to spin off their offerings rather than invest in necessary product improvements, based on the expense of obtaining the necessary clinical evidence. While the expenses of adopting the MDR and IVDR are high regardless of the size of the company, they are particularly difficult for smaller businesses.[37] IVDR compliance may be challenging for small-scale biotechnology businesses with restricted portfolios, and several kits may be discontinued.[38] As per Dr. Thomas Hafen "Big companies and authorities establish such a huge bar for entry that SMEs are forced to withdraw. Because it reduces competition and gives them competitive benefits, large firms play the regulatory game".

**Life cycle approach:**[39] The IVDR, in contrast to the IVDD, provides a greater impact on product life-cycle management and continual review.[40] Throughout the lifespan of a device, manufacturers should undertake performance evaluations and create, execute, record, and sustain a risk management system (Section 3 of Annex I) and a QMS (Article 10(8)). A proactive Post- Market Performance Follow-up (PMPF) strategy, which includes a post-market monitoring plan, is required from manufacturers.

**Increase in the cost:** The IVDR compliances have major cost and resource implications, the companies have to do barnstorming on reviewing the product portfolio, additional resources in terms of PRCC/quality assurance team for recertification conformity assessment process, developing performance evaluation report, clinical evidence, increasing transparency and traceability by incorporation of UDI, updating risk management and QMS. The time invested in meeting all the compliances results in the increase of costs to the final product.

**Increased scope for regulatory professionals:**[41] Each manufacturer is required to have a 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. As per Article 15 of IVDR, Each manufacturer is required to appoint a 'Qualified Person' responsible for Regulatory Compliance (PRRC).

**Increased transparency:** The establishment of EUDAMED (IVDR Article 33) is one of the important aspects of this rule, and it will be crucial in delivering comprehensive, reliable, and approachable data. The establishment of a UDI for each IVD device would improve tracking and boost post-market safety actions substantially.[42]

## CONCLUSION[43]

With the advent of new and more strict rules, the in-vitro diagnostic device industry is likely to undergo a major transformation. Due to a large number of revisions to prior directives, diagnostic device businesses are under pressure to complete substantial transition operations within tight deadlines. As a result, key stakeholders may perceive these developments as either an opportunity or a challenge.

### Changes that are seen as an opportunities

A. [44]The IVDR will enhance diagnostic testing quality across the EU, and its introduction is warmly received. As a result, to ensure a smooth and effective transition, it is vital to ensure that the appropriate infrastructure is in place before implementation.

B. [45]Thousands of new employments in the regulatory sector are expected to be created as a result of the new legislation. "Who's going to cover these expenses ?" says Thomas Hafen. Experts estimate that nearly 33 percent of all IVD enterprises will go out of business in the coming four years, or by the time IVDR transition period ends. "The "Top guys" will survive because they can absorb the additional expenses more readily than the "small ones" because of their financial muscle power."

C. "Following advancements need an open mindset with a readiness to communicate", says Peter Studer, coordinator of the Swiss Implementation Task Force. "Anyone can access it, including Notified Bodies and competent authorities, as well as manufacturers and other key stakeholders that provide diagnostic products. The continued growth of product transparency, which is what we promised the society today, will be ensured by the new EU regulations, he claims.

D. According to ShayestehFürst-Ladani, manufacturers can enhance their operations and optimize product portfolios as they assess existing product offerings in light of current advances so that they can manage to provide patient advantages and gain a competitive

edge. "It's evident that the new changes would make a dramatic shift in company future strategies and cause an additional financial strain, he said, but this will lead to the road of smarter innovations by adapting local conditions."

E. [46]According to the Porter hypothesis, the innovation impact will cause the development and implementation of environmentally friendly technologies and ecological advances, making industrial processes and products better effective.

F. [47]The fundamental goal of the IVDR, according to author Christa Cobbaert, is to promote openness, traceability, and efficacy of testing while still ensuring patient safety. The IVDR should be viewed as a means for better recording the safety and performance of tests in the real world throughout the course and product lifecycle. The main goal is to create a set of guidelines that are less susceptible to interpretation and that cover the whole lifecycle of device performance, rather than just the clearance stage.

**Changes that are seen as challenges**

A. Thomas Hafen, claims that as a result of this circumstance, "the industry for the diagnostic and medical technologies goods have degraded; due to the reduced competition and decreasing availability of innovative items".

B. [48]As Serge Bernasconi points out, "Whilst expenses of MDR and IVDR implementation are substantial regardless of firm size, they are particularly difficult for small and medium companies. On the other hand, these modest diagnostic device businesses are at the centre of innovation!" And with the changing environment financiers are losing their confidence for funding in innovative medical and diagnostic device sectors. They are now worried about the ability of Medtech inventors to place their brands on the market, he says. The price of placing a new product in Europe is escalating up!

C. [49]The healthcare sector is obviously experiencing major obstacles in deploying IVDR, with the possibility of thousands of IVDs being taken off the market and new product certification being greatly delayed, inhibiting innovation and adversely affecting patient care. If we extrapolate to the entire EU patient population and modestly predict that even 10% of the 34,000 CE-marked IVDs needing notified body involvement are not recertified by the date of application, we put thousands of European patient's health on risk, while the industry works to create the regulatory regime needed for successful execution.

D. [50]Based on our findings, we believe that a mere one-year deferral of IVDR may not be sufficient to assure patient management. As a result, additional more realistic approaches

may be required to break the deadlock and ensure a seamless and effective transition to IVDR with little impact on patients. "The implementation of the IVDR is highly welcome since it will improve the quality of diagnostic testing across the EU." Despite the fact that the new regulations and recommendations are still being implemented, key stakeholders like device makers, Hospitals, notified organizations, competent authorities, and pharmaceutical corporations are unprepared for this shift. ”As a result, it's critical to make sure the appropriate framework is in place prior to deployment to enable a smooth and an effective transition."

E. [51]The outbreak of coronavirus disease 2019 (COVID-19) has shown that laboratories' capacity to swiftly set up and operate LDTs is critical in responding to an emergent health catastrophe. The new regulations, on the other hand, might have a considerable influence on our capacity to react to a future pandemic since it restricts the use of LDTs. (All of the requirements that must be satisfied before an LDT can be utilised are listed in Article 5.5 of the IVDR.)

F. Despite the fact that the regulatory framework and recommendations are still being developed, important players such as device makers, health institutions, notified bodies, competent authorities, and pharmaceutical corporations are unprepared for this transformation.

G. [52]"Without revisions and contingency preparations, execution of the IVDR in May 2022 would take the healthcare industry into new waterways due to the EU regulatory infrastructure's unreadiness, writes author Christa Cobbaert. The European Commission has not conducted forthcoming risk analyses, but if nothing is done, it is expected that the repercussions will affect all stakeholders in the medical test pipeline, potentially harming patients and preventing practitioners from making proper clinical judgement due to the lack of diagnostic tests. Finally, it may deter companies and academic institutions from creating speciality tests, stifling medical diagnostic innovation’’

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