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New Era in Medical Device Regulations in the European Union

Raga Padmasri Deepika Majety, Sujatha Katru, Jaya Prakash Veluchuri*, and Ravi Kumar Reddy Juturi

Department of Pharmaceutical Regulatory affairs, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534202, Andhra Pradesh, India

Abstract

In Europe there are very high expectations regarding the quality, safety, and efficacy of medical devices. But in reality, it fails, due to many scandals that threatened the lives of thousands of people. So, the EU has introduced the new regulations in medical devices to meet the expectations. The old directives such as medical device directive (MDD) and active implantable medical device directive (AIMDD) are now replaced with medical device regulation (MDR), and *in vitro* diagnostic medical device directive (IVDD) is replaced with *in vitro* diagnostic regulation (IVDR). When compared to MDR there are more significant changes introduced in the IVDR. The New Regulations has a hard deadline for certifications and manufacturers cannot launch their product without certification, hence manufacturers have to meet the new regulations within the given time frame. The change in regulation brings a disturbance for the medical device industry. The manufacturers have to make strategic decisions to streamline their innovation pipeline and R&D processes in response to the increased cost of compliance and longer product certification time, so it is essential to conduct the SWOT analysis to evaluate the effect of new regulations. To bridge the gap between the new and old regulations, Gap analysis should be done. Gap analysis is used as a tool that helps to monitor the quality management system and is mainly useful where Standards and regulations are updated. This analysis may add value to reforming the portfolio. The regulatory authorities have to focus on the problems faced by manufacturers and try to resolve the issues as soon as possible.

Keywords: MDR • IVDR • SWOT • Gap Assessment

Introduction

The new medical device regulations in Europe have been reviewed and came into force in May 2017. The new regulation such as MDR/IVDR increases the traceability, transparency and patient safety which helps in increasing the quality and reliability of medical devices in Europe. The priority of new medical device regulation (MDR/IVDR) is patient safety. The existing directives such as old EU medical device regulations did not provide health care providers sufficient information regarding the scientific and technical details, safety and clinical performance of the medical device. The original suppliers were unable to track the devices due to inadequate device traceability within the supply chain and different EU countries interpreted requirements differently. These weaknesses were tries to resolve in the new medical device regulations. However, several patients have been suffered already from these weaknesses.

The New Regulations ensures the smooth functioning of the internal market of a medical device with a high level of protection of health for patients and users. To meet safety concerns of the device the MDR/IVDR has introduced stringent requirements in the areas of conformity assessment, post-market surveillance and through requirements to generate the clinical data which provides evidence of safety, performance, and adverse effects. Thus, these regulations set high standards in terms of quality and safety of medical devices which allows cost-efficient market access for an innovative medical device. According to the national requirements, the new regulations become more crucial in the development stage as it is required to develop and document the product [1-4].

***Address for Correspondence:** Veluchuri JP, Department of Pharmaceutical Regulatory affairs, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534202, Andhra Pradesh, India, E-mail: jayaprakashveluchuri12@gmail.com*

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Literature Review

The Revolution in the Medical Devices Regulations in European Union (EU)

In August 1994, the 93/42 EEC Medical Device Directive, published in July 1993, became national law; it created a European Union basis for quality and patient protection. Although the Directive has been steadily adjusted (the most extensive amendment to the MDD was made in 2007 with legal effect in 2010), the MDD framework remained outdated and unable to handle a large number of implants and software [5-7].

There are several kinds of events that triggered the evolution of regulatory reform in Europe:

- In August 2010 there was a recall of metal-on-metal hip implants due to the occurrence of the metallosis into the bloodstream. Metal-on-metal hip implant failures showing a weakness in the clinical evaluation and post-market surveillance requirements.
- June 2012 became known that Poly Implant Prosthese sold breast implants made with industrial-grade silicone instead of medical-grade silicone affecting about 300000 women. Fraudulent production of the PIP silicone breast implants highlighting the weakness in the legal system which damaged the confidence of EU patients, consumers and Healthcare Professionals.
- July 2011 U.S. FDA gave a warning regarding serious complications associated with surgical mesh for transvaginal repair.

Other reasons for (excessive) unsafe and ineffective medical devices on the European market are the risk level of the device is determined by the developer and not by the notified bodies and Notified bodies do not have personnel with expertise for each type of medical device. To make more profit NBs often do not reject requests of device developers. The CE-mark is granted

to the device even though there are no clinical investigations with high levels of clinical evidence and the finalized device is seen by a notified body one year after the CE-mark is granted. Moreover, the description of the device on paper is sufficient for granting a CE-mark by NBs. Finally, recall of a medical device does not make sense as similar devices will still be circulating on the European market. Even the original devices are banned but similar devices are still circulating in the market.

New Perspectives in European Medical Devices Regulations

MDR key changes: The new regulation will ensure fair market access for medical device manufacturers based on the following three main changes [8,9]:

1. Higher safety, quality, and reliability of medical devices
2. Higher transparency for customers
3. Enhanced vigilance and market surveillance

The new regulations do not need to be transposed into national law because they are already binding. This will lead to higher conformity in the understanding of the law across the EU market. However, extensive adaptations of existing national law will be required to be compliant with the new EU regulations. To create a consistent understanding between the EU and individual nations, the definition of a medical device has been slightly changed and associated terms were defined in a more detailed way (e.g. UDI, clinical evidence). To ensure a smooth transition, several transitional provisions are formulated and defined. The key changes in the MDR are as follows:

- General safety and performance requirements in annex I, identifies new conditions that will need to be addressed for CE marked devices under MDD. Recertify the existing products under new regulations.
- Most companies update clinical data, labeling, and technical documentation under new regulations. Manufacturers will provide in-depth clinical data to prove safety and performance data claims including tighter equivalence standards.
- Broadened the definition of medical devices includes non-medical and cosmetic devices that are not previously regulated. Examples included are products for cleaning, disinfectant or sterilization devices as well as a contact lens, liposuction equipment.
- Patients have access to safety-related information when Manufacturers will need to report all incidents, injuries and deaths in the EU portal. Report incidents that did not result in death or serious deterioration in health move from 30 days to 15 days.
- Companies undergo transition will need to revisit core processes including risk management, quality assurance and post-marketing. These processes are carefully reviewing, plan, and update in compliance with new requirements.
- Classification rules include active implantable devices, nanomaterials, and substances introduced into the body. Software is addressed in the new classification rule 11. Earlier there are 18 rues present in MDD, four new rules are added in MDR
- Conformity assessment procedures are changed compared to Annex VI of MDD. For some class IIa and most of class III devices, additional procedures must be followed and the notified bodies must consult expert groups.
- Essential requirements in MDD are renamed as 'essential safety and performance requirements' which are much more specific. Consequently, technical documentation is closely regulated. There is a comparison between MDD and MDR requirements.
- Manufactures must assign a unique device identification consists of the production and device identifier. UDI is not only the change to labeling requirements.
- Manufacturers must employ a person responsible for regulatory compliance. Other economic operators such as distributors, EU representatives, and importers have new roles.
- Unique device identification data and post-market data (example: PSUR) must be submitted to the EU database (EUDAMED).
- The clinical evaluation will be addressed on one page in MDD whereas post-market clinical follow up is not addressed. The MDR describes respective requirements in several articles and annexes.
- In MDD post-marketing surveillance is not specifically addressed but in MDR it is addressed specifically and regulated now.
- Due to lacking or insufficient harmonized standards, the EU commission entitles to introduce "common specifications". So far there are no harmonized standards and common specifications published.

IVDR key changes: The IVDR replace old directives (90/385/ECC) that were established well before the digital age [10,11]. In addition to bringing the regulatory environment up to speed on technology, they're designed to pave the way for better post-market surveillance, transparency, traceability, innovation, patient safety, and outcomes. They also create more uniform enforcement across EU member states and, overcome legal gaps, thereby supporting innovation and the competitiveness of the medical device industry.

- Based on risk, devices should be reclassified. Risk classes should be range from class A (low-risk devices) to class D (high-risk devices). IVDR uses a rules-based classification system. Classes A, B, C, and D. No more list of A, B, etc. (Chapter V & Annex VIII).
- More Rigorous clinical evidence. Clinical performance studies were conducted by manufacturers to provide evidence of safety and performance according to devices assigned risk classes. There are more requirements for clinical evidence and performance studies (Chapter VI & Annexes II, XIII, and XIV).
- Pre-market approval approach for self-testing and near-patient testing devices. There is new oversight of single-use IVDs, companion diagnostics, genetic tests.
- Increased post-marketing surveillance requirements and the timeline for reporting should be reduced. The vigilance and post-marketing Surveillance requirements are more stringent (Chapter VII & Annex III).
- Notified bodies reduce risk from unsafe devices by more rigorous surveillance.
- There are No "grandfathering provisions". Currently approved IVD devices as per MDD must be recertified under new requirements.
- Notified bodies review 80-90% of IVDs under IVDR compared to 10-20% review under IVDD.
- The definition of IVDs includes SAMD (Software as a Medical Device), software as part of IVD instruments, and apps are regulated.
- EU-based Authorized Representative (if physically located outside the EU) and a Person Responsible for Regulatory Compliance (PRRC) must be appointed by the manufacturer.
- Organizations have to establish, implement, document and maintain a risk management system. One should understand risk management as a continuous frequentative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall: identify and analyze the known and foreseeable hazards associated with each device.
- Provide information about warnings/precautions/contra-indications where appropriate, training to users.
- Manufacturers eliminate or reduce risks related to the use error and ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety).

- The labeling of identical or similar devices shall be distinguished and are placed on the market in both sterile and non-sterile conditions added to the symbol used to indicate that devices are sterile.
- Valid results should be provided for devices failure in case of self-testing and should be warned
- The UDI and Labels shall be provided in a human-readable format and may be supplemented by machine-readable information, such as radio-frequency identification or bar codes.

Transition timelines for legacy medical devices

To reflect the progress over the last few decades, the EU has therefore revised the legal framework [12-14]. Two new regulations are formed, one on the medical devices and another on IVD devices which were adopted by the council and the parliament and entered into force in May 2017. The new rules will fully apply after transitional period 3 years for MDR (up to 2020) and 5 years for IVD regulation (up to 2022) (Figure 1).

During the three-year transition period of the MDR regulation, medical devices are often placed on the market under the present EU Directives as well as the new regulation. This means that CE certificates issued under the current Directives will remain valid for 4 years post date of issue. Up to 25th May 2020, certificates under Medical Device Directive (MDD) are valid. From 25th May 2020 to 25th May 2024, certificates issued under the MDD, before the MDR fully applies, are going to be valid for up to 4 years up to 25th May 2024, devices in conformity with the MDR are often certified under the MDR and placed on the market From 26th May 2024 onward, devices placed on the market must be certified under the MDR (Figure 2).

The IVDR sets May 26, 2022, as a hard deadline for certification of IVD devices that didn't require certification under the IVDD. The devices cannot legally be sold without the IVDR certification after this date. However, IVD devices currently under NB supervision have a potentially longer transition period that extends to May 27, 2024. This transition period is based on already having a valid certification under the IVDD that extends past May 26, 2022 (but no longer than May 27, 2024). Furthermore, the sale of stored inventory is expected to be allowed as long as the IVD devices were produced under a valid IVDD certificate. Manufacturers without notified body certification after the transition period, and whose certificates issued according to the Directives are about to expire, may be unable to distribute products in the EU market.

SWOT analysis

The SWOT analysis framework is divided into two main categories, the

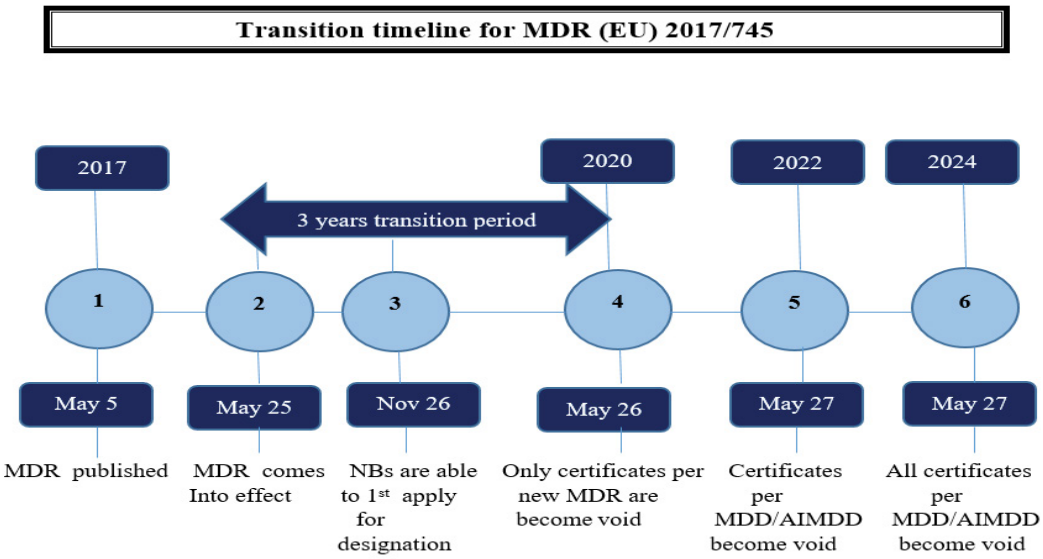

Figure 1. Transition timeline for MDR (EU).

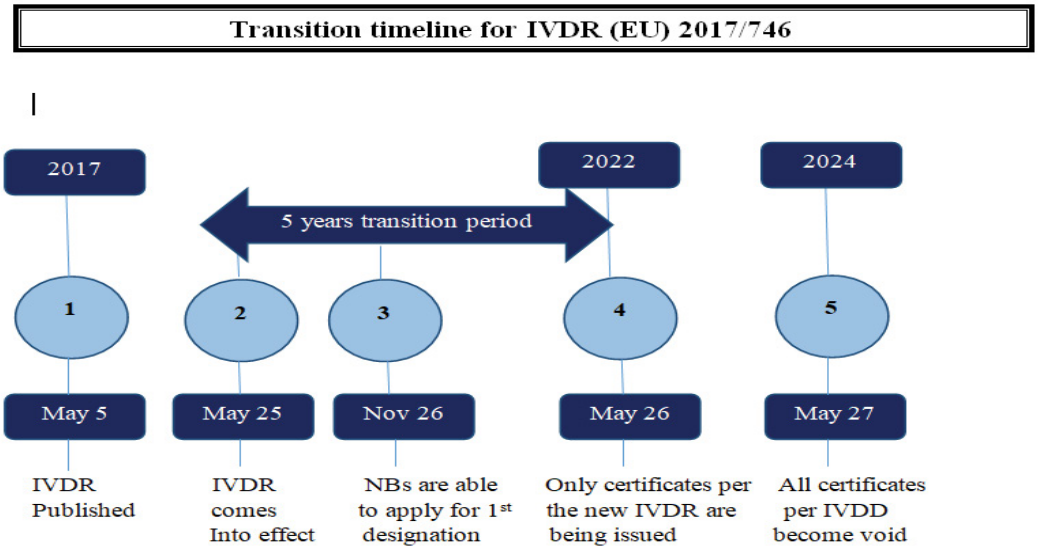

Figure 2. Transition timeline for IVDR (EU).

internal factors (internal strengths and weaknesses) and external factors (opportunities and threats) Strengths and opportunities are positive influences, whereas weaknesses and threats count as negative factors [15-17]. To evaluate the effect of the new MDR on the most stakeholders (i.e., manufacturers, regulatory bodies) a decision analytical framework has been applied by assessing the SWOT. The aim is to identify strategies that align, fit or match the resources and capabilities of an organization's strategic alternatives generated by a SWOT analysis is to build on the strength of an organization to exploit opportunities and counter threats and to correct organizational weaknesses.

Regulatory authorities

Strengths:

- Better Understanding Of risk-benefit ratio of the product.
- These regulations make Simplification & Integration of Processes easier.
- It enhances the Standardization and Consistency of the products with Improved Data Quality.
- Facilitates traceability in terms of health care finance and trade.
- It reduces Regulatory obligations in terms of safety and effectiveness.
- Facilitates vigilance and post market surveillance and clinical trials.

Weakness:

- It requires a high effort for a review of the evidence.
- It may lead to a Delay in the Assessment Process.
- To extend the resources in terms of handling complaints and negotiations, it requires a huge expenditure of money and time.

Opportunities:

- Granting Market Access of Products with Higher Quality for the benefit of the patient.
- It has increased the broader medical evidence.
- The companies have to provide maximum information about the product mainly on the safety and efficacy data as a part of the trail and this has open the doors of engaging the regulatory authorities, health care providers and professionals through outcome-based payment models.

Threats:

- Due to the increase in regulatory requirements, there is an increase in the cost of certain products.

Manufacturers

Strengths:

- It has provided Clear Rules in the product development process.
- It has improved regulations in terms of Efficiency.
- It paved a way for Enhancing Internal and External Collaborations between the regulators and manufacturers.
- It has Improved Data Integrity along with Standardization and Consistency of the product.

Weakness:

- Administrative work has increased due to structural adaptations such as new skills and expertise team.
- Increased Cost in Product Development and compliance of the information system.
- To meet the new EU rules, the companies have to spend a huge amount to full fill the organization and financial requirements and need to revise the product portfolio.
- To comply with the changes in the MDR/IVDR the companies have to readapt the products, documents, and processes.
- There is a lack of knowledge of the subject by stakeholders in the health institutes, service providers, companies.

Opportunities:

- Increased the chance for a successful market with high-quality products.
- Eased market trading in member countries.
- Increased developmental cost may also provide a platform for collaboration of both the large and small companies that can provide support and financing to take projects from proof of concept to market authorization.

Threats:

- There may be a chance of switching to alternative treatment by Physicians/Users.
- If medical product companies do not have a suitable notified body, it does not have many options. Either the company will be closed, sold or the company specializes in other things.

Gap assessment of MDR/IVDR for the manufacturers

Following steps needed to be performed by the manufacturers to do the gap assessment [18,19] (Figure 3).

Step 1 – Brief understanding the EU MDR and IVDR

One should have a good understanding of the new regulations, the scope and full impact on the business. Understanding the overlap and synergies with other applicable regulations and directives such as MDD, IVD, Clinical Trial Regulation (CTR) for human use, Falsified Medicines Act and Identification of Medicinal Product (IDMP) will be important.

Step 2 – Reforming of medical device portfolio

The portfolio of products should be fully reviewed and assessed against the new regulations and future requirements (Figure 4).

Financial: The new regulations which are implemented in the EU should require significant investment to plan and execute, especially for giant and mid-size medical device organization. It is necessary to understand how many products will we rationalize or divest and the impact of this on revenue and the percentage of revenue is at risk. Adoption of these changes is not optional and non-compliance will have serious implications on a company's license to operate.

Governance: A change of this magnitude will require cross-functional leadership and governance, both at the time of the new regulation for the strategical aspects and continuingly for the tactical and future implementation phases. The C-suite leaders will need to be very aware and become a driving force in the leadership and governance of this initiative.

Program and project planning: As medical devices organizations prepare to adapt and implement the new EU MDR, program and project planning are going to be crucial for fulfillment. Several tasks will need to be undertaken such as defining portfolio strategy and optimizing the portfolio. There need to

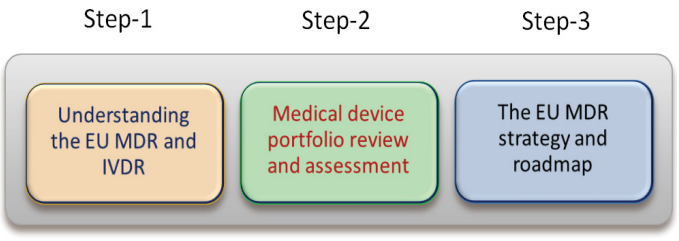

Figure 3. Gap Assessment of MDR/IVDR.

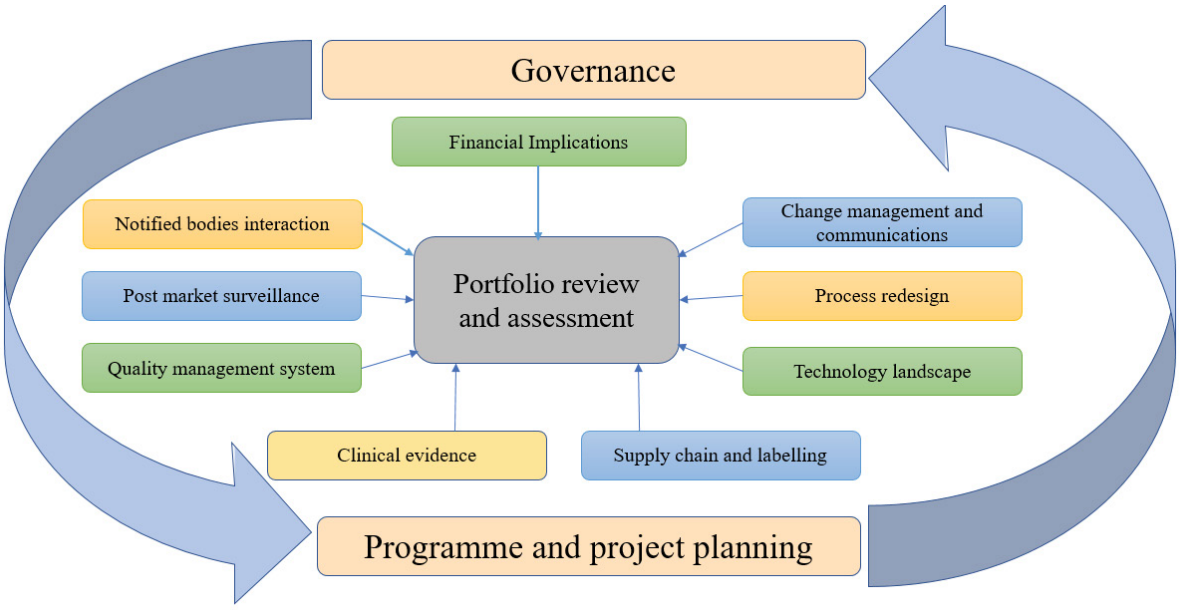

Figure 4. Portfolio review and assessment.

be good understanding about the new clinical evidence required for certain products, optimizing resource to be able to meet compliance requirements, adapting existing business processes to satisfy the new changes, building a successful roadmap and performing gap analysis to understand the present capabilities and future needs. To deliver such a difficult program, organizations will need strong leadership and program management skills.

Change management and communication: Change management and effective communication are going to be critical because the organization adapts to the changes. One should have to ensure whether there is the right number of resources to meet compliance.

Process redesign: The EU MDR requirements implementation plan will need to take into account documented procedures to be created, approved, and implemented for new and existing processes. The company authorities should have a check on the consistent processes and IT systems across the organizations.

Supply chain and labeling: The Company should have clear information regarding the structure of our supply network and how many resources shall be required to manage product label change to meet the new regulatory timeframe.

Quality management system (QMS): The new regulatory requirements require advanced quality systems which may require significant investment and also increased senior management involvement in both the upgrade process and ongoing management of the QMS. The company should upgrade the current QMS with the updated one and one should go for the ISO 13485:2016.

Notified bodies interaction: It is beholden on manufacturers to carefully assess go-to-market strategies, especially as they relate to moderate and high-risk devices. Given the number of Notified Bodies likely to seek designation, and the resources available for the designation procedure, the process to designate all Notified Bodies across the EU will be lengthy. There may be resource limitations during this process.

Step 3 – The strategy and pathway for EU new regulations

Once a full portfolio review and assessment has been performed around the current and future states, the gaps can be defined. These gaps would essentially be classified as strategic and tactical projects, prioritized based on business, legal, and regulatory drivers.

Assessment of current situation on new regulations

Progress to meet the requirements of the MDR/IVDR is slow [20]. At the half-way point in the transition period, even the largest and best-resourced manufacturers have completed only a handful of pilot MDR/IVDR technical les and are in the process of scaling up preparation. To put this into perspective, many MD/IVD manufactures can have hundreds or thousands of products required to meet the MDR/IVDR. Manufacturers are much further behind with their implementation plan than they were at the comparable time during the implementation of the MDD/IVDD, and many manufacturers have struggled to meet the transition deadline despite an earlier start. So, regulatory authorities need to solve these problems regarding the new regulations.

Discussion

The new regulations of medical devices (MDR/IVDR) in the EU are similar as well as quite different from their respective directives (MDD/IVDD). Manufacturers should examine the more crucial requirements in the MDR/IVDR to ensure that their systems and devices should comply with the new regulations. There is a drastic change in the regulations of the IVDs when compared to the medical devices and old directives. For example: earlier there are only 20% of IVDs comes under the notified body certification, now it has drastically changed to 80%. Therefore, the MD/IVD manufacturers must focus on the new regulations to establish and assess the gap between the current and new regulations to launch the product into the market. To make compliance with EU MDR/IVDR regulations is a difficult task for many organizations. Manufacturers must have a brief idea about the resources and what are the changes to implement in their portfolio to meet the new EU regulations. All the manufacturers must have to create a road map to meet the requirements. So, the manufacturer must need to review the guidelines thoroughly and have to find a way how quickly they can meet the requirements. So, manufacturers must have to create a transition plan for their devices with all the requirements present in the new regulations.

A strengths/weaknesses/opportunities/threats (SWOT) analysis conducted among the think tank participants shows real support for the objectives but also distinguish plenty of issues relating to the implementation of these tools. These new developments will have a major impact on the stakeholders of the medical device world that involves companies, health institutions, healthcare professionals, competent authorities, etc.

Conclusion

The trends happening in the medical device industry for the past few years are significant regulatory changes. The swift of regulations is in the spirit to achieve global harmonization. To achieve this objective it requires

major updates throughout many regulatory markets across the world. Many companies are facing difficulties to keep up with these keen changes due to a lack of adequate resources and internal initiatives to stay current with this tsunami of regulatory changes proactively. Those who are struggling most are reacting. They tend to delay, assuming there will be plenty of time to adopt the new changes. As an outcome, the results are, unfortunately, and all too often, slipshod and not thorough and well thought out for effective implementation. The companies who will thrive in this "new" era of medical device regulations realize that changes are likely to be the theme for the foreseeable future.

Conflict of Interest

The authors declare no conflict of interest.

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