WHITE PAPER

Breaking Barriers in Medical Device Development: The Convergence of Data and Regulatory Compliance

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The life sciences and healthcare sectors rank among the world's most tightly regulated industries, with a regulatory landscape that is constantly evolving. Globalization, rapid advances in science and technology, and the drive to improve patient outcomes and safety have fueled ongoing changes. Patient and consumer expectations are becoming increasingly sophisticated and demanding, with a greater emphasis on personalized, patient-centric experiences and the sharing of information about conditions and treatments. In clinical research, trial participants are now viewed as collaborators rather than mere subjects.

Adapting to new regulatory requirements is crucial for companies' commercial viability and reputation, and the ability to respond quickly and ef ciently is vital. However, the transition can be challenging, especially for companies with fragmented systems and siloed data that now need to be aligned and integrated.

This paper focuses on the ever-changing regulatory environment in the medical devices industry and the corresponding obligations that medical device organizations must comply with. Although the in-vitro diagnostics (IVD) sector has also undergone signi cant regulatory changes, it falls beyond the scope of this paper.

Medidata has identi ed several key themes in managing medical device data that are crucial to advancing product development, driving innovation, and improving treatments for patients and consumers.

The International Regulatory Standards Landscape

The global medical device market is governed by a signi cant and wide-ranging plethora of international, regional, and national regulations as well as device and equipment standards. Medical device standards allow institutions in the medical device eld such as product manufacturers, laboratories, and others to inspect and assess such equipment and devices to ensure standard quality and usability across operators. Some standards (non-exhaustive) key to medical devices and clinical research are outlined below:

- ISO 13485 is used for establishing conformity with quality system requirements to demonstrate the consistent delivery of the medical device that has been approved by the regulatory authority. ISO 14971 has become the benchmark for a medical device risk management process. Again, there are multiple standards in use. Some standards are used for all medical devices and other standards are based on the device type.

- ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice - ISO 14155 14155 is essentially good clinical practice (GCP) for medical devices and has had an overhaul with the latest version published in July 2020[1]. This standard is linked to other standards and regulations that address good clinical practice for the design, conduct, recording, and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. This standard somewhat harmonizes with the International Conference on Harmonization (ICH) GCP guidelines for the pharmaceutical industry, i.e., ICH E6 R2 GCP. There are similarities and differences between the two but fundamentally both provide clear guidance on designing, conducting, recording, and reporting results from clinical trials designed to assess the safety, ef cacy, and performance of drug and device products. The update to ISO 14155:2020 includes additions within the following areas:

  - GCP principles

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- Clari cations on requirements applying to each stage of clinical development
- Annexes relating to EU MDR
- Data requirements in monitoring & across the life cycle of the device development

- Electrotechnical Commission (IEC) - There is aligned collaboration and cooperation among the International Electrotechnical Commission (IEC), the International Organization for Standardization (ISO), and the World Health Organizations (WHO), who develop international regulatory harmonization initiatives to develop practical, effective and compliant medical device standards. IEC and ISO Standards are internationally recognized by medical device regulators. IEC prepares and publishes international standards for electrotechnology, such as the IEC 60601 which is widely recognized as the fundamental safety standard for medical electrical equipment. There are multiple standards with many common to any device but some are speci c to the medical device being produced.

In addition to these international standards, there are certain requirements which are regional and nation-speci c. Regulations and laws are not totally harmonized and vary between regions and countries. Navigating this can be a complex and time-consuming process.

Regional Perspective

UNITED STATES MEDICAL DEVICE DEVELOPMENT REGULATORY PROCESS SUMMARY

In the US, the Food and Drug Administration (FDA) is the institution responsible for regulating medical devices.

The determination of medical devices is variable depending on the regulatory region for market entry, but regulatory guidance is available to help navigate the decision-making process. The FDA makes resources available to help manufacturers understand whether a product is a medical device [2]. The decision is based on intended use and indications, such as products intended to diagnose, cure, mitigate, treat or prevent disease, or affect the structure or function of the body while not achieving its primary intended purpose through chemical action and is independent of being metabolized. Once it is clear that a product falls within the scope of a medical device, the next step is understanding the appropriate applicable product classi cation. Software can also be classi ed as a medical device, including "Software as a Medical Device (SaMD)" and "Software in a Medical Device (SiMD)," and a digital navigator [3] can be used to determine if a particular software is a medical device.

The FDA uses a risk-based classi cation system that groups medical devices into three categories, Classes I, II, and III. Class I is associated with the lowest risk and Class III is the highest risk [4]. The requirements for each classi cation vary. There are key regulatory areas that govern medical devices in the US, which are outlined below and not exhaustive:

- Establishment Registration & Medical Device Listing - Both manufacturers and distributors have to register with the FDA to be able to introduce their devices to the market.

2 https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device
3 https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-policy-navigator
4 https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device

- Premarket Noti cation 510(k) - Premarket noti cation is required for most, but not all medical devices. If a device requires the submission of premarket noti cation, it cannot be commercially distributed in the United States until it receives an authorization from FDA. The FDA has nalized its guidance on the “Electronic Submission Template for Medical Device 510(k) Submissions,” this will require medical device manufacturers 510(k) to use the FDA’s electronic Submission Template And Resource (eSTAR) format. This becomes effective as of October 1, 2023.

- Premarket Approval (PMA) - Premarket Approval (PMA) is a risk-based evaluation process designed for devices that pose a high threat to patients' health. Manufacturers of Class III devices (and devices that are not substantially equivalent to Class I or Class II) are required to submit a premarket approval application.

- Investigational Device Exemption (IDE) - allows manufacturers to use the device in question in clinical studies to collect evidence that proves its general safety and effectiveness. Data gathered during IDE-related studies is typically used to support a PMA.

- Quality System Regulation - The Quality System Regulation includes requirements related to methods, controls, and facilities used for the designing, manufacturing, labeling, packaging, storing, purchasing, installing, and servicing of medical devices.

- Labelling - Labeling regulations lay out the requirements for the labels on the device and the descriptive literature related to the device.

- Medical Device Reporting - Medical Device Reporting (MDR) has been established in order to help FDA and manufacturers identify and monitor the negative effects of a speci c device in a timely manner. All deaths or serious injuries must be reported to the FDA under the MDR program.

- Unique Device Identi er (UDI) - The Unique Device Identi cation System, commonly referred to as UDI, is a Food and Drug Administration (FDA) rule that requires medical device labelers to mark medical packages and devices with a unique barcode.[5] There are different compliance policies and rules for each device type. FDA has now published their updated policy regarding Global Unique Device Identi cation Database (GUDID) submission requirements for certain Class I devices considered consumer health products.

The FDA has been modernizing some of these processes and requirements to ensure they keep up to speed with the rate of scienti c and technological change. [6]

Due to an increase in violations over the past years, regulatory authorities have increased scrutiny of data integrity. The FDA de nes data integrity as “the completeness, consistency, and accuracy of data which should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.” The integrity of data generated by medical device manufacturers is critical. Correctly recorded and complete information is the basis for manufacturers to ensure product identity, strength, quality, and safety. Data integrity builds the foundation for creating safe medical devices.

The FDA provides guidance and continues to focus on cybersecurity device design, labeling, and the documentation that it recommends be included in premarket submissions for devices with cybersecurity risk. This ensures that marketed medical devices are suf ciently resilient to cybersecurity threats.

5 https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identi cation-system-udi-system

6 https://www.fda.gov/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities

In addition, Software as a Medical Device (SaMD) opens up new possibilities in healthcare. The healthcare industry is being transformed by this technological breakthrough, and there is a tendency toward deploying AI-ML-based technologies in the medical device eld. The FDA's Digital Health Center of Excellence has outlined an action plan [7] with operational guidance for both SaMD and software in a medical device (SiMD), which proposed a tailored regulatory framework for AI-ML-based SaMD, Good machine learning practice, Patient-centered approach incorporating transparency to users, and Regulatory science methods related to algorithm bias and robustness.

Another example of regulatory modernization is the FDA's Real-world evidence (RWE) program, a critical step in modernizing the medical device industry by enabling the evaluation of medical devices' safety and ef cacy using real-world data (RWD) in addition to clinical trial data. The FDA's RWE program also allows for continuous monitoring of medical devices using data from various sources and can quickly identify potential safety concerns. By incorporating RWE, the FDA can evaluate the performance of medical devices across a diverse patient population and clinical settings. Medical device manufacturers can leverage existing RWD sources to reduce the time and cost of clinical trials, accelerating the regulatory process and facilitating quicker access to innovative medical devices for patients.

On December 29, 2022, The Consolidated Appropriations Act was signed which included the Food and Drug Omnibus Reform Act, (FDORA). The legislation contains information under Chapter 2, 'Mitigating shortages', which includes information on the registration of foreign device manufacturers, combating counterfeit medical devices, and a section on preventing a shortage of medical devices [8]. The bill also contains provisions on medical devices, including outlined scenarios for dual submission for certain devices, and ensuring cybersecurity in medical devices that can be referred to as cyber-devices, with cybersecurity vulnerability monitoring plans required.

MEDICAL DEVICES REGULATION IN THE EUROPEAN UNION

The regulation of the medical device industry in Europe has remained stagnant since the 1990s. Howeverope has reLp0.15sd),0 (ed t)10 (o

The European MDR classi cation system is similar in outlining medical device classes, ranging from low-risk class I, medium to high-risk class IIa, IIb, and high-risk class III [13]. The requirements for devices of higher risk are more stringent, for obvious reasons of safety.

However, due to COVID-19, as of April 2020 the European Commission[14], has adopted a proposal to postpone by one year the date of application of the Medical Devices Regulation to allow Member States, health institutions, and economic operators to prioritize the ght against the coronavirus pandemic. [15]

As of February 2023, the European Parliament has of cially approved the transitional period modi cations following an overwhelming vote on a proposal by the European Commission. The proposal comes as a result of the risk of the original transition timelines potentially leading to medical device shortages, and an attempt to preserve patient access to medical devices. In the proposal, the European Commission acknowledges that despite great efforts, the capacity of conformity assessment noti ed bodies remains insuf cient to meet the original transition timeline for the volume of medical devices [16]. If noti ed body approvals were to continue on the current trajectory, then all 8,120 devices can be transitioned from Directive to

- Improving traceability of data - The EU MDR will ensure vital information is easy to nd through more stringent traceability measures. For instance, patients will receive an implant card with all the essential information, and a unique device identi er will be mandatory for every product. A unique device identi er will be mandatory for every product.

- Transparency of data - the European Commission will establish a centralized European database for the storage of information on medical devices, called EUDAMED. EUDAMED is a multipurpose system structured around 6 modules concerning stakeholder and UDI registration, noti ed bodies and certi cation documentation, clinical investigations and performance studies, vigilance, and market surveillance. This will facilitate the communication of both pre- and post-approval product information between economic operators, the Commission, EU Member States healthcare professionals, and the public.

- Clinical Performance Studies and Clinical Evidence - The EU MDR will require device manufacturers to conduct clinical performance studies and provide evidence of safety and performance, proportionate to the risk associated with a given device. The new EU MDR will lead to changes in the medical device development process due to new clinical evidence requirements. Additional clinical evidence will also be required for products already on the market. An understanding of the impact on R&D and the ability to retain products on the market and launch products in the pipeline will be crucial.

- Risk-based classi cation system - A new system has been developed for risk classi cation in accordance with international guidelines. While the classi cation system (Class III, Class IIa, Class IIb, and Class I) will be retained, some rules have been strengthened. This may result in a signi cant number of product types previously exempt from the regulations now being included in the scope

- Post Market Surveillance System (PMSS) - As part of their quality management system, manufacturers must also establish a PMSS, which should be proportionate to the risk class and the type of device in question. Manufacturers will have to report all incidents, injuries, and deaths into an EU portal that will contain relevant data, so patients have access to safety-related information.

- Greater enforcement and governance and tighter controls - The new requirements will impose tighter pre-market controls on high-risk devices and apply a more rigid approach to the conduct of both clinical evaluation and the clinical investigation of clinical trials. EU cross-border clinical trials will be subject to a single coordinated assessment. Stricter requirements on the use of hazardous substances will also be introduced, and device manufacturers will be required to collect and retain post-market clinical data, as part of the ongoing assessment of potential safety risks.The EU MDR is placing further responsibilities on the noti ed bodies, now being subjected to heightened scrutiny from competent authorities. Noti ed bodies have to be designated under the EU MDR, with the process of designation coordinated at a European level. In addition, noti ed bodies may conduct unannounced audits to manufacturers.

- Introduction of an Expert Panel - Under MDR's Article 106, an expert panel will be introduced with the aim of impartial and objective performance evaluation and device risk review. The panel will be independent of noti ed bodies and manufacturers.

European Union Medical Device Approval Process

The EU medical device approval process is initiated when a foreign manufacturer designates a Person Responsible for Regulatory Compliance (PRRC), who acts as the primary liaison between the manufacturer, noti ed bodies, and national competent authorities. The sponsor must determine the category of the device in question.

For Class I, non-sterile, and non-measuring devices, a Quality Management System (QMS) is not formally required, though a Post-Market Surveillance (PMS) procedure is necessary, which is not audited by a Noti ed Body. For devices belonging to other classes, a QMS is required, and most companies seek compliance with the ISO 13485 standard. The manufacturer must prepare a technical le to demonstrate compliance. For class III devices, a dossier must be compiled. The QMS and technical le (dossier for class III devices) must be audited by a Noti ed Body. There is no audit or technical le required for class I, non-sterile, and non-measuring devices.

Medical device manufacturers must also prepare a declaration of conformity, with certi cates issued by noti ed bodies being valid for a period indicated on the certi cate, which cannot exceed ve years according to Article 56 of the MDR. Should a noti ed body discover that any of the MDR requirements are not being met, the certi cate of conformity will be suspended or withdrawn. The manufacturers of all medical devices in the EU must be prepared for audits and extensive post-market surveillance and must register with the Noti ed Body and register the Unique Device Identi er (UDI) on EUDAMED.

Impact of EU MDR on Medical Device Approval

The EU MDR has posed signi cant challenges to the medical device industry, primarily due to a shortage of designated noti ed bodies. This has resulted in a substantial increase in the duration and cost of reviews for recerti cation, which at this early stage of embracing the newly introduced pathway for medical device approval, is posing a transitory challenge to the industry. However, similar to all new regulatory standards, the novel period of adjustment is usually a learning curve and becomes more familiar and less burdensome with time. The introduction of new regulatory frameworks is always accompanied by embracing innovation and the ambition to improve the health and safety of the population.

AI in Medical Devices

Arti cial Intelligence (AI) is increasingly being adopted in the medical industry and recent technological breakthroughs have resulted in many medical devices incorporating AI functionalities. In the forthcoming future, AI will be regulated by a cross-sectoral EU AI Act[17], which has been proposed and is expected to encompass a wide array of high-risk AI systems, such as those that are integrated into medical equipment. Beyond the legal framework governing AI devices, data-focused regulations such as the proposal for the European Health Data Space will enable manufacturers to access a wider range of health data from EU Member States, thereby facilitating the development of more effective devices.

The AI Act from the European Commission is a cross-industry regulation proposal that adopted a common position at the end of 2022[18]. Some of the conformity assessments and further requirements that will impact medical devices with AI elements and their manufacturers and might result in duplicative compliance requirements to those already imposed by EU MDR. This medical device ecosystem needs to be carefully monitored, and industry is calling for alignment with sectoral legislation so as not to introduce duplicative assessments on medical device manufacturers, which is already subject to stringent regulations [19]. In an ideal world, the regulatory framework from cross-industry and the medical device industry should be complementary.

UK MEDICAL DEVICE REGULATION

The UK's Medical and Healthcare Regulatory Agency (MHRA) is the authority responsible for medical device regulation, including market surveillance, decisions over supply and marketing, as well as the designation and monitoring of UK conformity assessment bodies. Since the UK's departure from the EU, the medical device regulatory environment, including device certi cation, conformity marking, and device registration have all been revised in Great Britain (England, Wales, and Scotland) under the secondary legislation of amendment of medical device regulation of 2019 [20]. As of January 2021, there have been signi cant updates on the path to market of medical devices in the UK. While the European CE marking and certi cates issued by EU-recognized noti ed bodies will be recognized in Great Britain until June 2023, the new UKCA (UK Conformity Assessment) marking [21] is the updated route to market for medical devices entering the market, where UK

Where the market launch plan includes both Great Britain and the European market, it is important to note that the UKCA marking is separate and is not recognized in the EU, where a CE marking is the equivalent requirement. Until June 30, 2023, both UKCA and the EU CE marking can be utilized to place a medical device on the Great Britain market. However, after July 1, 2023, entering the Great Britain market will only be possible with the UKCA mark.

All medical devices will require MHRA registration as a prerequisite for entering the market in the UK. Where the medical device manufacturer is not established in the UK, the MHRA registration is to be facilitated by a manufacturer-appointed UK Responsible Person. Upon entry to the UK market, a vigilance report needs to be submitted to the MHRA as appropriate if device-related incidents occur.

For medical devices targeted for UK entry, it is important to be aware of the differences in requirements in Great Britain (which consists of England, Wales, and Scotland) and Northern Ireland, the latter hosting a set of distinct rules under the Northern Ireland protocol [22]

Typically, companies have several challenges when effectively leveraging data to foster product innovation.

Structuring and standardizing data – Most data within a company and its associated ecosystem are fairly unstructured, which means it must be converted into structured data which can be a very manual resource-intensive process, prior to

Summary - A bRAVE/Bold New World

The Life Sciences and Healthcare industry is undergoing signi cant transformation as advancements in science and technology continue accelerating. As highly regulated sectors, it is crucial for regulatory frameworks to adapt and incorporate changes in a controlled manner to ensure patient safety and promote public healthcare.

Regulators are taking bold steps to modernize and update current frameworks amidst the constantly changing regulatory landscape, particularly considering the current global situation. The EU MDR regulations prioritize patient-oriented