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WHITE PAPER

The Regulatory Evolution and Data Revolution in Medical Device Development

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The Life Sciences and Healthcare industries are among the most heavily regulated industries in the world. The regulatory environment is continuously changing. Change is driven by globalization, accelerated advancements in science and technology coupled with an ability to advance cures for patients, improve patient safety leading to avoidance of unnecessary incidents. There is an ongoing rise in the sophistication and demands of patients, consumers and regulators. As patients' and consumers' expectations evolve, they are demanding a more patient-centric experience and more information shared regarding their conditions and treatments. Trial participants will be seen as collaborators in clinical research rather than subjects. The life sciences and healthcare industries are going through a period of unprecedented regulatory change impacting pharmaceuticals, medical devices, in-vitro diagnostics and healthcare organizations for the benefit of patients. The ability to respond to regulatory requirements swiftly, effectively and efficiently is vital to both a company's reputation and viability commercially. The transition from current requirements to new requirements can be challenging, especially for companies with disparate systems and data sets that are siloed and now need to be aligned and aggregated.

This paper looks at the current, dynamic regulatory landscape within the medical devices sector and some of the current and future changes medical device organizations will need to adhere to. The in-vitro diagnostics (IVD) sector is also going through regulatory change - a topic that is out of scope for this paper.

Medidata looked at some of the themes of which management of medical device data is critical to driving insights and accelerated product development which brings innovation and new treatments for patients and consumers.

The International Regulatory and Standards Landscape

The global medical device market is governed by a significant 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 field such as product manufacturers, laboratories, and others to inspect and assess such equipment and devices to ensure standard quality and usability across the operators.

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 standards for medical electrical equipment. There are multiple standards with many common to any device but some are specific to the medical device being produced.

ISO also has internationally accepted standards for the medical device industry for example, 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 would be used for all medical devices and other standards based on the device type.

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

Clearly, having robust regulations and laws in place ensures the supply of quality consistent, safe, efficacious devices. The regulatory environment is dynamic and evolving; new regulations are seeking to harmonize and simplify the rules simultaneously improving patient safety, product traceability, data quality and consistency and transparency demanded by patients and the public.

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 FDA uses a risk-based classification system which groups medical devices into three categories, Classes I, II and III. Class I is associated with the lowest risk and class III the highest risk. The requirements for each classification vary. There are key regulatory areas that govern medical devices in the US, these 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.
- **Premarket Notification 510(k)** - Premarket notification is required for most, but not all, medical devices. If a device requires the submission of premarket notification, it cannot be commercially distributed in the United States until it receives an authorization from FDA.
- **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, labelling, packaging, storing, purchasing, installing, and servicing of medical devices.
- **Labelling** - Labelling 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 specific device in a timely manner. All deaths or serious injuries must be reported to the FDA under the MDR program.

The FDA has been modernizing some of these processes and requirements to ensure they keep up to speed with the rate of scientific and technological change.[1]

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

In addition, due to an increase in violations, regulatory authorities have increased scrutiny on data integrity. The FDA defines 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. Essentially data integrity builds the necessary foundation upon which to create safe medical devices.

European Union Region Regulations

The regulation of the medical device industry in Europe has been relatively static since the 1990's. However, due to a number of patient safety incidents in the EU, urgent regulatory and compliance reforms to the industry were initiated and executed.[2] [3]

Among the most significant of these are the European Commission's 2012 proposals for regulation on medical devices (EU MDR) and in-vitro diagnostics (EU IVDR).

- EU MDR Regulation (EU) 2017/745 of the European Parliament and of the Council of April 5, 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC[4]

- EU IVD Regulation (EU) 2017/746 of the European Parliament and of the Council of April 5, 2017 on in-vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.[5]

The new regulations apply after a transitional period. For medical devices this being three years after entry into force of the EU MDR regulation and five years for EU IVDR. However, due to COVID-19, as of April 2020 the European Commission, 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 prioritise the fight against the coronavirus pandemic.[6]

The impact of these regulations and associated operational aspects has had a significant repercussion on the landscape for the operations of medical device manufacturers, importers, distributors and health institutions and generally economic operators. Most organizations have been preparing for this transition for many years. The cost of compliance has been significant to prepare for and the reality of all this work to implement will only be proven well beyond a year from now.

2 https://ec.europa.eu/growth/sectors/medical-devices/new-regulations_en
https://webarchive.nationalarchives.gov.uk/20141206151729/http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON143784

3 https://www.theguardian.com/science/blog/2012/feb/29/hip-implant-fiasco-regulatory-failings

4 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745

5 https://eur-lex.europa.eu/eli/reg/2017/746/oj

6 https://ec.europa.eu/commission/presscorner/detail/en/ip_20_589

The EU MDR, and the breadth of medical devices to which it applies, has been significantly expanded and includes certain products which previously did not fall under the definition of a medical device. Some key elements of the new legislation include:

- **Enhanced vigilance and market surveillance:** Once devices are available for use on the market, manufacturers are obliged to collect data about their performance, and EU member states will coordinate more closely in the field of market surveillance.

- **Improving traceability of data** - The new regulations will ensure vital information is easy to find through more stringent traceability measures. For instance, patients will receive an implant card with all the essential information, and a unique device identifier will be mandatory for every product. A unique device identifier 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, this is called EUDAMED. This will facilitate the communication of both pre- and post-approval product information between economic operators, the Commission, EU member states and, in some cases, 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 with 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 ability to retain products on the market and launch products in the pipeline will be crucial.

- **Risk-based classification system:** A new system has been developed for risk classification in accordance with international guidelines. While the classification system (Class III, Class IIa, Class IIb and Class I) will be retained, some rules have been strengthened. This may result in a significant number of product types previously exempt from the regulations are 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 rules 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 will place further responsibilities on the notified bodies, being subject to heightened scrutiny from competent authorities. Notified bodies need to be designated under the EU MDR, with the process of designation coordinated at a European level. In addition, notified bodies may pay unannounced audits to manufacturers.

The new EU MDR rules support patient-oriented innovation and take particular account of the specific needs of the many small and medium sized manufacturers in this sector. There will be clearer rules in place to enable harmonization, standardization and support simpler and less complex trading between EU member states

In general, the new EU regulations and also the FDA regulatory evolution aim to modernize and strengthen patient safety and public health, by introducing greater supervision and surveillance, traceability, transparency and risk-based classification system for medical device equipment.

Revised ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice

ISO 14155 is essentially good clinical practice (GCP) for medical devices and has had an overhaul with the latest version available May 2020. 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 Harmonisation (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, efficacy and performance of drugs and devices products. The update to ISO 14155:2020 includes additions within the following areas:

- GCP principles
- Roles and responsibilities
- Clinical quality management, clinical investigation audits and ethics committees
- Risk-based monitoring requirements
- Clarifications 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

Regulatory Common Themes - It is all about data!

Regulators are trying to keep pace with science and technology and there are common themes across the evolutions and there are solutions to address the changes. If you step back from the detailed guidance and consider the common themes in general there is an all-round greater emphasis on:

- Patient safety and centricity
- Data standardization
- Generation of greater amounts of clinical evidence data and the ability to aggregate and submit
- Data quality and data integrity
- System integrity and validation
- Improved traceability
- Improved transparency
- Integration and alignment of multiple data sets for regulatory submissions

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 aggregation, integration, and analysis. Advances in statistical processes help clean and/or analyze unstructured data.
- **Combining multiple datasets** - Integrating data from disparate datasets can provide novel insights. Managing data from different platforms and data streams can be overwhelming, extremely resource intensive, and costly. Errors and oversights can cause frustration, loss of valuable data, and even compliance issues.
- **Data ownership and privacy issues** - Major concerns have been raised over privacy, confidentiality, and control of patients' data once it is acquired. In general, individuals are increasingly concerned about data breaches, the implications of data analytics, and transparency over the control of data ownership. Furthermore, when it comes to acquisition of data from a variety of sources, there are additional vulnerabilities regarding data privacy since the data are often accessed and utilized by a multitude of data scientists, often via vulnerable open-source technologies. Overall, these risks must be managed at the level of the medical device company.
- **Leveraging data to support medical device supporting auditing, regulatory inspections and positioning commercially**
    - Capturing a wider variety of non-traditional clinical data derived as close to the source as possible, including electronic health records, imaging data, sensor data, and patient-provided data
    - Establishing the ability to aggregate data quickly based on standards and governed data management
    - Serving analytical reports and dashboards to the broad audience for analysis and collaboration

The huge volume of information demands an infrastructure that can assure that the data are reliable and not siloed.[7]

With rapid innovation in medical devices, it is essential that regulatory innovation follows. Globally regulatory agencies recognize the need for regulations to evolve and adapt, and these agencies are continually implementing new models to generate clinical evidence and other data sets to strengthen product quality while safely improving patient outcomes.

Having complete control and unification of data can help drive insights, facilitate and foster innovation and flex compliantly to a dynamic regulatory environment. Utilizing big data in an efficient and meaningful manner requires up-front planning and investment in the infrastructure and data alignment and integration. Once the appropriate infrastructure has been established, the struggles of dealing with huge volumes of information are minimized, and manufacturers can focus their efforts on bringing life-changing medical devices to market. The organizations with the best control of their data and unifying systems have the capability to provide faster insights and can accelerate product development faster - outpacing the competition.

Making this a Reality with Medidata

MEDIDATA RAVE CLINICAL CLOUD™

Medidata's SaaS-based platform, the Medidata Rave Clinical Cloud, offers the scalability, configurability, and sustainability required by medical device and diagnostic clinical trials. Scale trials from small or specialty start-ups to global multinational companies all while accommodating different classes of devices from pre- to post-marketing studies. The Medidata Rave Clinical Cloud is the cutting-edge platform that transforms and unifies the clinical trial experience for patients, sponsors, CROs, and research sites. Designed as a unified data platform, the Medidata Rave Clinical Cloud creates a single source of truth for all study-related data. Simply put, enter data once and let the platform master and populate it throughout the end-to-end suite of Rave applications. Optimize operational execution, decrease the data entry and maintenance burden, and reduce the number of clinical systems across your study teams.

CONNECTED PATIENT PLATFORM - FROM ACORN AI, A MEDIDATA COMPANY

Every day, hospitals, doctors, and life science companies collect huge amounts of data on individual patients, diseases and medical procedures. The rise of a new generation of robotic, precision, and surgical devices has created vast stores of video, imaging, and other electronic surgical notes, while the proliferation of digital patient technologies, such as electronic medical records, wearable sensors and mobile apps are generating an inventory of personalized data on each patient. Connect the new digital health data ecosystem and enable collaboration and precision in patient care with Acorn AI's Connected Patient Platform.

The Connected Patient Platform unifies disparate data sources such as imaging and medical device data, hospital data, e.g., EMR, PACs, RIS, and other clinical data from across the healthcare ecosystem into a central hub, driving better patient care. The Platform connects all appropriate stakeholders and ensures they have access to the right patient data in the right format at the right time. Acorn AI's Connected Patient Platform is the engine that helps healthcare providers collaborate for better, more precise, delivery of care. By automating workflows and collecting, aggregating and modeling data from a wide range of health sources in a standardized, multi-faceted data set that enables deep real-world analysis to help physicians gain valuable insights about the treatment and outcomes of their patients.

7 https://www.medidata.com/en/resource/whitepaper-201704-the-rise-of-integrated-data-in-medical-devices/

Summary - A Bold New World

The Life Sciences and Healthcare sector is going through significant change, over the years science and technological innovation have set an accelerated pace. As highly regulated industries, it is essential that regulatory frameworks adapt and embrace change to take advantage of these innovations in a controlled manner for patient safety and public healthcare.

Regulators are making bold steps to positively modernize and renovate existing frameworks in the ever-changing regulatory landscape, especially in light of the current, global situation. One example of this is the European Medicines Agency Strategy 2020-2025, which is very broad and deep. They have five key goals of which one is around 'Catalyzing the integration of science and technology in medicines development', focusing on creating an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products.[8]

A common underlying theme with many of the new regulatory requirements is about unlocking the power of the data and the execution of best in class data management procedures. This is multi-faceted, revolving around use of standards to drive consistency and quality and the alignment and aggregation of quality data sets coupled with data analytics to drive insights. This is challenging with siloed data sources and disparate systems.

The organizations with the best governance and control of their data, with unifying collaborative infrastructures have the invaluable capabilities to provide faster insights and confidence through greater intelligence for decision making. In turn this can accelerate product development and an agility to adapt to new regulatory frameworks - outperforming the competition and not just having a competitive advantage but also high reputational public profile.

8 https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy

About Medidata

Medidata is leading the digital transformation of life sciences, creating hope for millions of patients. Medidata helps generate the evidence and insights to help pharmaceutical, biotech, medical device and diagnostics companies, and academic researchers accelerate value, minimize risk, and optimize outcomes. More than one million registered users across 1,400 customers and partners access the world's most-used platform for clinical development, commercial, and real-world data.

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