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Medicare Rule-O-Rama

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THE INCREASING ROLE OF PATIENT SAFETY IN DEVICES AND COMBINATION PRODUCTS in the European Union

>>Shweta Agarwal, PhD, Paula Burge, and Chris Holmes, Navigant

The Medical Device Regulation takes effect in less than a year and that means some big impending changes for how companies run their post-market surveillance and vigilance programs. Experts from Navigant dig into the implications for industry.

To ensure better protection of public health and patient safety, the European Union adapted a series of stricter regulatory frameworks and compliance requirements for medical devices.

As the May 26, 2020, deadline for the new Medical Device Regulation (MDR 2017/745) compliance approaches, medical device companies must get up to speed on what's changing, challenges to anticipate, and how to transition effectively to compliance. The sweep of the reforms is broad ranging. This article provides an overview of the major changes, factors to assess and overcome, and guidance on creating an optimal process, with a special emphasis on post-market safety monitoring and reporting requirements.

MDR Fundamentals

The MDR differs significantly from the existing Medical Device Directive (MDD) and affects the quality assurance, clinical data, technical documentation, post-market plans and surveillance activities, and product labelling. Specifically, the new legislation:

- Reinforces the criteria for the designation of notified bodies and processes for their oversight.
- Introduces stricter pre-market control of high-risk devices.
- Strengthens clinical and post-market surveillance (PMS) requirements.
- Improves transparency through establishment of EU database on medical devices (EUDAMED) and traceability requirements based on Unique Device Identification (UDI)
- Adds pro-active reporting requirements after commercialization.
- Increases roles and responsibilities for all economic operators.
- Expands the definition of "medical device" to include software, non-medical and cosmetic devices that are similar in function and risk profile to medical devices, listed under Annex XVI, even if they do not have an intended medical purpose.

What this means in practical terms for manufacturers is many legacy products will need to be recertified, many devices will be reclassified as higher risk, and devices in development will be held to a more rigorous approval process. (*See "Raising the Class I Alarm: How EU MDR Impacts Low-Risk Device Manufacturers," this issue.*)

Importantly, because the new MDR legislation is formed as a "regulation" rather than a "directive," the EU law is directly applicable at a national level without requiring transposition through specific national legislation of the individual 28 member states. This should allow for greater legal certainty, and prevent variation in the approach taken or in the rules relating to medical devices.

Manufacturers should carefully consider the impact and financial implications of meeting the new requirements, and plan early for the transition. Market access will require companies to conduct deep portfolio audits to determine the impact on margins, assess unique device identifier readiness, relabel products, and ready data for public release. It all adds up to complex change program and high remediation cost. Meaning, from an operational viewpoint, companies can anticipate a costly path to compliance.

Associated Risk Levels

Considering the level of risk associated with a device, its intended use, and maturity stage (i.e. is this a novel device where a post-market clinical study is to be conducted or is this a low-risk device with a long history of clinical performance where the risks are well understood?), manufacturers may need formal mechanisms to collect specific types of information from specific sources. The need for information can vary significantly. Accordingly, companies will need to tailor information-gathering mechanisms to the device in question, the environment in which it is used and its users as appropriate for the need.

For reference, in the MDR, Article 83, which addresses the PMS system of the manufacturer, clarifies expectations: "1. For each device, manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device. That system shall be an integral part of the manufacturer's quality management system (QMS) referred to in Article 10(9)."

That is, it is up to the manufacturer. Having said this, the post-market surveillance report approach should be proportionate to the risk class for the device, substantiated by a sound, well-supported methodology. In particularly, the manufacturer should:

- Identify potential sources of input for post-market surveillance, e.g. post CE-clinical trials including PMCF, incidents, customer surveys, complaints, user feedback, service reports, in-house testing, failure analysis sales contacts, databases, literature, device registries, etc.
- Establish collaborative, cross-functional efforts with clinicians to answer targeted questions to understand the accuracy of benefit-risk estimates, or whether new, off-label uses are occurring.
- Analyze techniques, e.g. trending with defined cut off points, trigger values related to certain characteristics, etc., and triggers for certain actions, e.g. starting a field safety corrective action, issue a design change, etc.

In addition, the "benefit-risk" determination is new to the MDR, and the current EU guidance on medical device clinical evaluations (MEDDEV 2.7/1 revision 4) provides supporting information. Nevertheless, manufacturers should consider reviewing whether the benefits associated with a device are clearly understood and documented, as this is needed to understand—and will impact—the benefit-risk requirements throughout the MDR.

Vigilance for Medical Devices

Manufacturers will be required to report all incidents, injuries and deaths into an EU portal that contains relevant data, so patients have access to safety-related information. Article 10 of MDR explains the general obligations of manufacturers, while Chapter VII of MDR explains the post-market surveillance, vigilance and market surveillance requirements.

Further, this regulation dictates that manufacturers of devices (other than exempt investigational devices) must establish, document, implement, maintain, keep up to date, and continually improve a quality management system that ensures compliance in the most effective manner and in a manner that is proportionate to the risk class and the type of device.

In short, the requirement is to integrate post-market surveillance with the quality management system. The global QMS standard ISO 13485:2016 has created separate, identified subclauses for these two activities. ISO 13485 considers complaints and reporting to regulatory authorities to be one of the mandatory inputs in management review (in the scope of clause 5.6.2 (b) (c)) and defines the procedural requirements of complaint handling and reporting for medical device suppliers (clauses 8.2.2 and 8.2.3). Therefore, these procedures are elements of the manufacturer's QMS.

A Field Safety Corrective Action is used to reduce the risk of death or serious deterioration in the state of health associated with the use of a medical device already on the market. Such actions are notified via a Field Safety Notice. The new regulations make minimal changes to this process, so manufacturers will not have to update their reporting systems.

However, the new regulations update the requirements for vigilance—the identification, reporting and trending of serious incidents and the conduct of safety-related corrective actions—to make them more rigorous. The current two-day deadline is retained for reporting a serious public health threat, as is the 10-day deadline for reporting a death or serious health deterioration. However, the reporting deadline will be reduced from 30 days to 15 for reporting all other serious incidents (Article 87).

In addition, the MDR requires manufacturers to submit vigilance reports to a centralized pan-European database (Article 92), rather than to the individual national Competent Authorities. This central EU database is not likely to be available before the year 2020, so national vigilance reporting procedures likely will remain in place for a while, including for medical devices registered under the new MDR.

Vigilance for Combination Products

Under the current MDD, if a product comprised of a drug and a device constituent part is governed by the Medicinal Products Directive 2001/83/EC, the device constituent part needs to fulfill certain aspects of the MDD 93/42/EC (i.e. Annex I of the directive). This typically includes device development activities—such as requirements engineering, design verification, human factors engineering, and others. These need to be documented in specific device files, which may or may not become referenced or included in the regulatory dossier for the medicinal product.

For the first time, under the new legislation, devices that are integral with a drug product will require notified body assessment. The key concept is the Medicinal Product Directive (MDP) continues to be the governing regulatory framework for the combination product as described above. However, Article 117 of the MDR has amended the MDP 2001/83/EC to necessitate the involvement of a device regulatory body. This means a notified body must review the device part of the regulatory dossier, and provide an opinion on whether this part fulfills Annex I of the MDR, i.e. compliance with the General Safety and Performance Requirements, based on the evidence presented in the dossier.

This change affects medicinal products that incorporate a device that would be covered by the MDR if supplied separately. The dossier for a marketing authorization under the MPD will have to include evidence of the conformity of the device part with the applicable general safety and performance requirements in Annex I to the MDR. This could be either:

- An EU declaration of conformity or the relevant certificate issued by a Notified Body that allows a CE mark to be affixed to the device; or
- An opinion on the conformity of the device with the general safety and performance requirements in the MDR.

The intent of this new regulation is to increase the safety and performance of the device constituent and the combined product itself.

Checklist for COMPLIANCE

Companies manufacturing a medical device must meet new obligations set out in the MDR to ensure:

- The device has been correctly classified against the new risk classification criteria [Annex VIII of the MDR and In Vitro Diagnostic Directive (IVDR)];
- General safety and performance requirements are met, including for labeling and technical documentation and quality management systems (Annex I of the MDR and IVDR);
- Increased requirements for clinical evidence are met (Annex XIV of the MDR and IVDR);
- A representative responsible for regulatory compliance is in place (Article 15 of the MDR and IVDR);
- Economic operators in the supply chain are compliant;
- Sufficient financial coverage is in place with respect to potential liability (Article 10 of the MDR and IVDR); and
- The new vigilance reporting timescales are met, and an annual periodic safety update report is created (Chapter VII, Section 1 and 2 of the MDR and IVDR).

Single Complaint and Reporting Process

The procedures for complaint handling and reporting of incidents are elements of a manufacturer's quality management system. ISO 13485:2016 has created separate, identified subclauses for these two activities.

When the need to report to an appropriate regulatory authority is identified, the manufacturer is required to implement documented procedures for: 1) reporting adverse events that meet reporting criteria, 2) providing trend reports, and 3) reporting field safety corrective actions to regulatory authorities. They also need to keep records of such reports. That means manufacturers are required to establish, implement and maintain documented procedures for handling complaints in a timely manner. Considering the changes in the regulations, manufacturers likely will face an increase in the number and types of reports submitted. Therefore, implementing a single complaint and reporting process will be a challenge to accommodate and address all the changes in a timely manner.

The deadline for transition to ISO 13485:2016 passed in March 2019. Also, in regard to the requirements for vigilance, MDR includes information previously contained in guidance "MEDDEV 2.12-1—revision 8—Guidelines on a Medical Devices Vigilance System." Therefore, manufacturers are expected to prepare for MDR by 2020.

Getting Ready: Factors to Assess

Manufacturers are well advised to begin preparing and implementing changes to ensure compliance and alignment of processes and systems as soon as possible. Companies need to fully understand what the MDR means for their businesses, including how it will impact internal processes and external factors.

Documentation processes: Manufacturers must determine how to accommodate compliance, knowing their new reality largely revolves around generating and curating vaster volumes of more detailed documentation. As such, they should review their entire portfolio to assess what necessary documentation they have in place and what needs to be created. For example, because the MDR emphasizes clinical evaluation requirements, real-world clinical data must be collected and maintained. So, manufacturers should be sure the required data and documents—such as post-market surveillance plans and reports, post-market clinical follow-up reports, periodic safety-update reports, and summaries of safety and clinical performance—are all in place.

Systems: Manufacturers need to review their existing systems to be sure they can support clinical, quality, and regulatory requirements across the organization. For example, do their current systems help improve compliance, mitigate risk, and provide increased visibility and transparency across the organization? If not, then upgrade and improve systems. In either case, manufacturers can take advantage of the new legislation as an opportunity to transform technology for a competitive advantage. Consider adopting new systems that provide a framework for more collaborative and transparent document and data management across all functions.

As the new legislation comes into effect, medical device manufacturers should follow an optimal process for compliance:

1 Create and follow a proactive and comprehensive system to gather experience from the use of devices to meet MDR vigilance requirements. This system should:

- Enable cooperation on vigilance and market surveillance.
- Connect with corrective action or preventive action processes.
- Enable update of technical documentation, including the risk-benefit determination and clinical evaluation.
- Be part of the manufacturer's QMS.

2 Provide sufficient resources—including personnel and budget—to create an effective compliance program that ensures requirements for post-market surveillance and vigilance are met. The compliance officer should be someone dedicated to and well-versed in compliance, and be positioned as a partner, not an arbitrator. The officer and/or compliance representatives should be permanently and continuously available.

3 Implement a post-market surveillance system for collecting information and characterizing the safety and performance of the device, or family of devices, and the methods and processes to assess the collected information. As part of the QMS and technical documentation, this system should:

- Incorporate information from complaint investigation and market experience.
- Describe methods to monitor trends, identify statistically significant increases in frequency or severity of incidents, and provides trend reports.
- Define methods of communication with competent authorities and notified bodies.

- Define methods of communication with authorized representatives, importers, distributors, users and patients.
- Describe the means of tracing and identifying devices.
- Reference the documented procedures for post-market surveillance, periodic safety update reporting, as well as processes for corrections, corrective actions or preventive actions.

4 Develop a post-market surveillance report that summarizes the results and conclusions of the analysis of the PMS data, including the rationale for and description of any preventive action or corrective actions taken. Updated this report as necessary and make it available to the competent authority upon request.

5 Develop a Periodic Safety Update Report that summarizes the results and conclusions of the analysis of PMS data with usage data. This should be kept up to date throughout the lifetime of a device, and be part of the technical documentation. Specifically, the report should be updated for devices as follows:

- Class IIa: as necessary and at least every two years;
- Class IIb: as necessary and at least annually, made available to the notified bodies and upon request to the component bodies;
- Class III: as necessary and at least annually;
- Implantable and Class III devices: as necessary and at least annually. Submit electronically through EUDAMED to Notified Body, and add any details from the Notified Body evaluation and any actions taken. Make the periodic safety update report and the notified body evaluation available to competent authorities through EUDAMED.

6 Keep in mind, to enhance patient safety, more products and more incidents—now including low-risk ones—fall under the vigilance requirements. In addition, the timeline for reporting serious public health threats has changed to within two days; and all other events to 15 days. Reporting death or unanticipated serious deterioration in health have remained unchanged at 10 days.

Editor's Note: This is one of two articles exploring key changes to post-market surveillance reporting requirements. Here we look at what's in store for companies in the European Union. In the second piece, we will explore a new voluntary medical device reporting program in the US.

SHWETA AGARWAL

Shweta Agarwal, PhD (shweta.agarwal@nagivant.com), is a senior consultant at Navigant. Her areas of expertise include European CE marking, technical file documentation, clinical evaluation reports, risk-management files, vigilance, and device classification in markets worldwide.

PAULA BURGE

Paula Burge is a managing consultant with Navigant with over 20 years of experience in regulatory compliance and quality systems in the medical device and combination product spaces.

CHRIS HOLMES

Chris Holmes is a director and manages Navigant's EU Regulatory Practice. He has over 20 years' experience in delivering strategic advice and implementation and his expertise includes regulatory affairs and compliance, drug safety, risk management and operational performance programs for pharmaceutical, biotechnology, medical device and consumer health.