by GLORIA CRISPINO, PhD

MDR: It's Not the End of the World for Medtech Companies

The new MDR heralds the beginning of a more regulated era in the medical device industry and with that come concerns about the requirements and costs that it imposes. Chief among the many potential consequences is that US and European medtechs may no longer look to Europe first to get CE mark and begin commercialization. But MDR doesn't have to strike fear in the hearts and minds of medtech executives. Here are proven tools that companies can employ in order to ensure a smoother and less costly transition to the new MDR system.

The new EU Medical Device Regulation (MDR), which is set to become effective on May 26, 2020, has sparked an uproar of worry throughout the medtech industry regarding the increased time and costs that the new rules will impose. High on the list of concerns is that the new rules will result in companies no longer looking to get CE marking for innovative technologies and introduce them in Europe first, meaning European patients will lag behind those in other nations in getting access to these life-saving devices. Some of industries' concerns are warranted, in part by the inefficiencies and stumbles that have characterized the lead-up to the new MDR's implementation. These include a slower than announced process for re-certifying Notified Bodies (NBs) and delays in bringing the European Database on Medical Devices (Eudamed) online.

But it also should be noted that some of the concern is simply the result of a new regulatory system being put in place, which is bound to cause upheaval even under the best of circumstances—as the expression goes, the devil known.... Upon closer look, the reality for medtech companies may not be the disaster many are predicting if they employ certain strategies in advance to help manage this transition. This article outlines several approaches that companies can take to minimize the disruption of MDR.

The Changing Landscape of the Medtech Industry

The Medical Devices Directive (MDD) 93/42/EEC and the Active Implantable Medical Devices Directive (AIMDD) 90/385/EEC were introduced in 1992 and have served the medical device industry well, helping to create a single market for medical devices in Europe. Although the MDD and the AIMDD were effective in creating a single market, they had their limitations and did not withstand changes in the medical and technology fields, thereby highlighting the need for new regulations. Directive 2007/47/EC modified the MDD and the AIMDD to address these issues; however, the resulting amendment did not fulfill all requirements.

The European Union Commission published proposals for the new European Medical Devices Regulation, MDR 2017/745 and the European In Vitro Diagnostics Regulation (EU), IVDR 2017/746 in September 2012. Almost two years later, in April 2014, substantial amendments for the proposed MDR and the proposed IVDR (347 and 254 amendments, respectively) were released by the European Parliament. The European Council responded to these adapted proposals in September 2015. The European Commission considered the differences in the versions of the regulations to be so great that they facilitated negotiations ('trilogues') between the European Parliament and the European Commission. As the result of these discussions, a compromise text was produced in June 2016, with the regulations formally published in the Official Journal of the European Union in May 2017, and the subsequent official translational period to last from 26 May 2017 until full implementation of the MDR from 26 May 2020. Certificates to the MDD or AIMDD may be issued up to May 26, 2020 and remain valid until expiration or May 25, 2024, whichever is earlier.

The new regulations have been described as the most disruptive change in regulations ever faced by the medical device industry in Europe. They have raised the level of accountability on claims to an unprecedented level of rigor for medical devices, requiring evidence-based results to support clinical, performance and safety claims. This new requirement is now as stringent as some of the US Food and Drug Administration regulations for pharmaceuticals and medical devices. Compliance with these regulations will require hundreds of millions of euros for the medical device industry.

The introduction of more stringent clinical data requirements, including the provision of sufficient evidence,

extended data management, more complex conformity assessment procedures (particularly for high-risk medical devices), and product liability and penalties in the MDR will change the regulatory environment in Europe. There is already concern from the NBs that they will not be able to complete all the additional work created by the MDR and this may affect access of compliant devices to the European market.

Shift to a Life-cycle Approach

Up to now, the medical device industry has differed greatly from the stringent expectations of pharma. According to ClinicalTrials.gov, there are currently over 200,000 clinical trials registered for pharmaceutical drugs compared with only 50,000 for medical devices. The main purpose of the new medical devices regulation for Europe (MDR 2017/745), in contrast to the MDD, is to encourage a shift from the pre-approval stage (i.e., the path to CE marking) to a life-cycle approach, similar to that endorsed by the FDA. The MDR is transforming medical device clinical research in Europe, closing the gap between the medical device and pharma industries.

The MDR places greater emphasis on clinical data and clinical evaluations than the MDD. Furthermore, the MDR, but not the MDD, provides a definition of clinical evaluation, as follows: "'clinical evaluation' means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer."

Demonstration of clinical safety or performance of medical devices will be far more challenging under the new regulations, with equivalence, which is currently used to justify references to studies conducted with other devices, more rigorously interpreted. In contrast to the current MDD regulations, clinical investigations will be expected for implantable Class III devices as the equivalence approach will generally no longer be accepted by NBs.

Key Changes and Scope of the Proposed MDR

Key changes in the proposed MDR include introduction of special procedures for NBs for certain high-risk devices and manufacturers' liability; strict rules for clinical investigations and alignment to the Clinical Trials Regulation; reprocessing of single-use devices is allowed only under specific conditions, and carcinogenic substances and substances with other potential high-risk effects on the human body can only be used together with a strictly defined justification.

The definition of a medical device in the MDR is significantly expanded compared with that in the MDD: products for cleaning, disinfection, or sterilization of devices will now be considered as medical devices, rather than accessories to medical devices, and are included in the scope of the MDR.

The relevant safety and performance requirements for all medical devices will remain applicable, whether or not they are within the scope of the MDR alone or also included in other directives or regulations.

The MDR also distinguishes between the responsibilities of the authorized representative (AR), and those of the distributor and the importer. The AR and the manufacturer are made jointly and severally liable for defective devices, with the importer also sharing liability according to Product Liability Directive 85/374/EEC. These liability requirements may affect the willingness of manufacturers, ARs and importers to share information with competent authorities (CAs).

Device Identification, Classification, and Databases

The MDR introduces mandatory unique device identification (UDI) to facilitate device traceability. Each medical device will be assigned a device identifier (DI) and every production series or batch will be given a production identifier (PI).

Classification of devices under the MDR is similar to that under MDD; however, thorough assessment of all devices is recommended. Classification changes under the MDR include surgical meshes, non-viable tissue of human or animal cells, and active therapeutic devices with an integrated diagnostic function that provides data on patient management, which will be considered Class III; devices intended for inhalation of medicinal substances will be considered Class IIa or IIb, and software can be included in any risk class.

Data pertaining to clinical investigations, product registration and vigilance will be entered into Eudamed and other databases to enable an exchange of information between national CAs and the European Commission.

Clinical Evaluation and Investigation

The MDR introduces new and stricter criteria for demonstrating equivalence and more extensive data are required from clinical investigations of the devices. Data for each claim must be robust and valid but, in contrast to pharma, does not have to be from randomized controlled trials (RCTs). Different approaches can be used, e.g., animal studies and clinical studies with different design approaches to RCTs.

Clinical investigations for implantable and Class III devices are needed unless there is a good reason not to do these. For example, a manufacturer with a new device that is a modification of another device (and this modification is confirmed by the NB) may rely on the clinical data for this other device provided technical

documentation is available; or the device is currently on the market, has been used for years with no major issues, and is considered compliant with requirements for clinical data. Manufacturers of implantable and Class III devices may voluntarily consult an expert panel before the clinical evaluation. The scientific review of clinical evidence by the NB should be considered a useful methodological tool rather than a threat.

Article 83 of the MDR defines the requirement to collect and analyse information about incidents and adverse events, trend reporting, relevant literature, information from users and publicly available information about similar devices. Therefore, the MDR brings the medical device industry into closer alignment with the pharmaceutical industry in terms of true postmarketing surveillance, building a systematic collection of data, with a rigorous structure of active data collection rather than passive collection of warnings.

The NB is required to send a clinical evaluation assessment report for Class III implantable devices and Class IIb devices intended to administer and/or remove a medicinal product to the relevant expert panel (through the EU Commission) (Annex IX, Chapter II, Section 5.1). If the expert panel issues an opinion on the application this is done within 60 days. Expert panel costs may be covered by fees paid to the EU Commission by the manufacturer.

Implementation of the MDR

The early implementation of the MDR in the transition phase until late 2019 comprised large companies and small and medium-sized enterprises (SMEs); from late 2019 to May 2020, early adapters will include more large companies, some medium companies and more innovative SMEs; from May 2020, all large companies and all SMEs will have adopted MDR, with complete engagement by May 2022 (see *Figure 1*).

To put this transformation into context requires consideration of the scale of the transition in Europe. There are 27,000 medical device companies in the EU, 95% of which are SMEs, with approximately 750,000 devices in the market and 500 Class III devices patented per year.

Important Considerations in the MDR Transition

Important considerations moving to MDR include:

Extensive data requirements. All the manufacturer's claims, whether they are clinical, performance or safety, must be sustained with sufficient evidence, i.e., valid data and valid methods of analysis must be provided to support the veracity of the claims.

1. *Higher standards for acceptable data.* Clinical evidence is now a pillar for regulatory submissions. This means that the manufacturer must provide data on the clinical risks and benefits of the device as part of the submission.

2. *Expanded regulatory scope.* Safety and performance of a device is assessed on the product full life-cycle, from research and development (R&D) to clinical to postmarketing surveillance. This implies that the manufacturer must provide evidence for each product life-cycle phase.

3. *Limited response time.* The MDR will be effective on May 2020 (May 2022 for IVDR). All renewals for the manufacturer's devices currently on the market and all new devices must be compliant with the new regulations by this date. There is no grandfathering rule.

4. *Bottlenecks and cascading delays.* There are currently fewer than 10 NBs to process the full medical device industry that sells into Europe, with the number of NBs expected to grow to 20 to 30 over time. Each NB will have its own process and schedule to bring MDR applications for review. A high submission volume combined with limited NB staffing resources will slow the process for medical devices early in the queue and will compound into significant delays for medical devices submitted later. The manufacturer must be prepared to enter the queue early and strategically.

5. *Compliance costs may shape the business model.* Uncertainties on the transition process are impacting the assessment of portfolio reductions. The manufacturer will need to prioritize which medical devices enter the queue first, later, and possibly not at all.

Possible Approaches to Implementation

The MDR focuses on clinical and safety and establishes the requirement for 'sufficient evidence' to support each claim for each medical device. If there is insufficient evidence and further data are unavailable, the claim would have to be dropped. If there are lots of potential claims (e.g., 100-250), all of which are unique statements on safety, performance or engineering, supportive data are required for every single statement and this is very time consuming, so prioritizing the statements is essential. Possible approaches to managing implementation of the MDR include a regulatory-driven approach that focuses on compliance; a business-driven approach that concentrates on the value of the device, and a biostatistical, quantitative, data-driven approach that comprises acquiring and scoring evidence for claims.

The Regulatory Approach to Implementation

The regulatory approach to implementation comprises a nonquantitative assessment of the overall regulatory submission. IQVIA has launched an IQVIA *SmartSolve* Enterprise Quality Management Solution (EQMS) that provides expanded quality, regulatory, and safety compliance support for the MDR. This includes support for the new Manufacturer Incident Report (MIR) requirements and timelines, enhanced design control functionality, and expanded risk management capabilities.

TÜV SÜD AG has developed MDR conformity assessment procedures, with step-by-step information for each of the procedures and an overview of the procedures for different device classes and types as well as relevant surveillance activities.

According to a recent survey by ICON, 41% of respondents reported their companies' transition to MDR and IVDR was still in the very early planning stages, with no respondents reporting a nearly complete transition plan. The most important challenges cited by these companies were clinical evidence generation, postmarketing surveillance and technical documentation. ICON suggested that companies will need to go beyond the expertise of regulatory experts and product managers and create an interdisciplinary team that includes business strategists and executives, who may be called upon to develop a new business plan to meet the strategic changes and resources required for effective MDR transition.

ICON outlined the following steps that the medical device industry must address promptly to maintain market share and develop and maintain financially viable product portfolios: overcoming the growing shortage of NBs; addressing new clinical data requirements under MDR and IVDR; developing a global market entry strategy to capitalize on opportunities; considering launching new products in the US and other countries, and involving top management in compliance efforts. Manufacturers were recommended to act quickly to identify and secure an NB, ensuring they evaluate expertise and resources to determine which NBs are the best fit for their products. ICON offers a full range of services that can help manufacturers as they face the complexity of the new EU regulations, from regulatory and market strategic analysis to the specifics of developing clinical evidence and successful regulatory submissions.

The Business Approach to Implementation

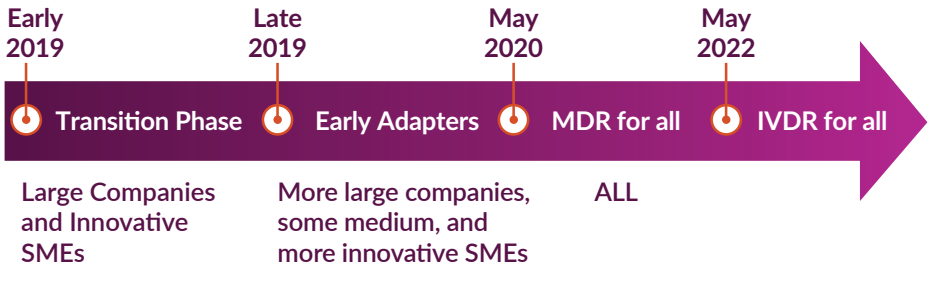
The British Standards Institution has developed a BSI Compliance Navigator to enable manufacturers who are subscribed to the service to navigate the MDR transition. The BSI's Smart Support has been designed to help the subscribing manufacturer to understand the impact of the new regulatory changes to enable the business to more easily navigate the transition and implement the new requirements. Each Smart Support topic has been written by an industry expert and reviewed by a topic expert and advisory panel, providing an executive summary suitable for senior management, detailed practical guidance on what has changed and what this means for the organization, actions to take now and a summary of what is still to change. There is also advice on AR liability, and economic operators, such as the roles of the AR, the importers/distributors, and the kit assemblers, as well as guidance on clinical data requirements, UDI, postmarketing and classification changes.

The Biostatistical Approach to Implementation

The evidence required by the MDR necessitates the ability to measure evidence for the intended use of the medical device. One approach to the MDR transition is to measure and score the robustness of the evidence. The fundamental logic behind this approach is that although any claim could be proposed, only the claims that have valid supportive evidence should be considered. One of the most interesting discoveries when using this approach through the MDR transition is that the amount of data available is huge. In laboratory studies, animal studies, preliminary first-in-man studies and postmarketing surveillance trials, the amount of information gathered about the use of the devices is significant and unprecedented. The real issue is not the lack of evidence, it is how this evidence could and should be used to support the claims. This is why a rigorous biostatistical approach can be an invaluable tool to effectively navigate the MDR submission.

Quantitative gap analysis has often revealed that the data gap is small. Previous studies by StatisticaMedica have

Figure 1
The MDR Transformation Cycle: The Players



Source: StatisticaMedica

shown that most organizations already have up to 80% of the data needed for submission, and perhaps all of it if a device is far along in development or already on the market. The MDR does not specify the type of study or number of studies required to back a claim. This is a key point as any and every source of data on the medical device can be explored, including extracting new data from different sources or reanalyzing old data. The data may be hidden, but there is no restriction on using it provided it is methodologically and statistically valid. This approach maximizes the value of the data already available to the manufacturer.

The statistical logic of regulatory biostatistics can create a methodological flow and a synergistic, lean, waste-free environment where data have a purpose and they follow a journey, from the intricate wiring pulses of the cables, chips, and novel materials during the R&D process to the clinical outcomes we measure when we use that sophisticated set of cables and chips and materials on a human being.

Adopting methodological processes based on assessing the validity of the data, enable claims and evidence to be robust, relevant and comparable.

With these methods, the claims are evaluated to show which have evidence and to identify the claim-specific gaps in the manufacturer's data to produce a score on 'likely MDR compliance' in the current status. A set of algorithms is used that searches and assesses statistically-robust methods, clinically-relevant outputs and regulatory-valid data. Benefits of this approach include device selection that is evidence based, and a methodological assessment that supports the business decision by providing an indication of how strong are the data by family of devices and by therapeutic area.

> *The MDR is complex and implementation of this regulation is a huge and impactful challenge for the medical device industry. A new biostatistical approach like the one described here turns the MDR 'upside-down', with specific claims rather than generic requirements leading the submission.*

The medical device industry could be described as being lost in the woods or not seeing the forest for the trees. The assumption may be that portfolio cuts and large, rigid trials will be needed, and delays in product approval will be inevitable. This does not have to be the case. Efficacy and traceability of evidence are key. A methodological roadmap can be developed that guides the collection of data and helps navigate the complexity of the evidence gathering process. Simplicity and statistical logic go a long way. Utilizing these types of processes simplifies the MDR approach.

Gap analysis, in which the validity of current data is assessed to ensure it is statistically robust, clinically relevant and methodologically comparable; new investigations, in terms of study design, statistical analysis plans (SAPs), methods and analysis to create valid, MDR-compliant evidence, and data integration will occur throughout the full product cycle, from pre-clinical to clinical to postmarketing, and the new clinical evaluation report (CER) for the device would include and align all this evidence.

Approaching the MDR from a biostatistical perspective will provide new insight and a pragmatic, feasible, and financially and scientifically sound implementation of the new regulations.

Regulatory biostatisticians can and have creatively tamed the power of biostatistics in a regulatory environment and, in liaison with the regulatory affairs, clinical and marketing teams, can ensure that everything that can be done in a regulatory environment is achieved to enable the manufacturer to build as strong a case as possible for their device. This multidisciplinary strategy to test the robustness of the device data has been proven to reduce the waste and 'noise' of submission.

Using Biostatistics to Turn MDR Upside Down

The MDR is complex and implementation of this regulation is a huge and impactful challenge for the medical device industry. A new biostatistical approach like the one described here turns the MDR 'upside-down', with specific claims rather than generic requirements leading the submission. By staying 'close to the device,' this approach reduces the need for new evidence to the minimum required, enables informed and strategic prioritizing of medical devices and enhances the chances of successful, timely submissions. The approach also reduces waste and minimizes costs across the entire medical device development process, from the R&D stage to clinical to postmarketing. The impact of the MDR is enormous, but there is no need to panic. There are solutions that are obvious to us, but perhaps surprising to most players in the industry. These new biostatistical approaches are a proven, effective, valuable addition to the regulatory armamentarium.

Gloria Crispino, PhD, cStat (Gloria.crispino@statisticamedica.com), is the founder and CEO of StatisticaMedica Ltd., (www.statisticamedica.com). She has over 20 years of experience in conducting clinical research and consulting, both in academia and industry, in Europe and the US.

Editorial assistance for this article was provided by Brigitte Scott, PhD, Consultant Medical Writer for StatisticaMedica.

>>Key references for this article online at mystrategist.com/market-pathways.