How to Prepare for the EU's New 2020 Medical Device Regulation

Your EU Medical Device Regulation Guide

Big changes are underway for the European market and how it regulates medical devices with the recent unveiling of the Medical Device Regulation MDR 2017/745. This regulation replaces the long-standing Medical Devices Directive (MDD) 93/42/EEC, specifically MedDev 2.7/1 for medical devices, which was created in 1992 and most recently updated to Revision 4 in July 2016. The MDR is a significant deviation from the MDD and MedDev 2.7/1, and it is important to implement necessary changes to how one conducts literature searches, post market surveillance (PMS), and post market clinical follow-up (PMCF) in the 2017-2018 timeframe to be prepared for MDR by 2020. The following article is a set of guidelines for making this transition smoothly.

<u>European Single Market and Medical Devices</u>

The European Single Market has 28 Member States of the European Union (including the UK), the European Economic Area (Liechtenstein, Norway, and Iceland), and Switzerland (through bilateral treaties). The purpose of the European Single Market is to allow free movement of goods from one Member State's market to another, assuming the following three criteria have been met:

- Essential requirements for the products involved have been defined;
- Methods that describe how product compliance with the requirements have been established, and;
- Mechanisms to supervise and control the actions of those involved in manufacturing and distributing the product have been created.

To address these criteria, the Medical Devices Directive (MDD) 93/42/EEC was created in 1992 and was most recently revised in 2009 (Revision 3) and 2016 (Revision 4). However, the MDD has some inherent weaknesses that make interpretation of the directives inconsistent across the Member States, which allowed some defective products to be released into the market. In addition, the roles of the Competent Authorities and numerous Notified Bodies were unclear, and the enforcement of the directives across the Member States was haphazard.

While attempting to address these weaknesses, it became clear that the MDD could not be revised sufficiently to correct the directive, and so a new document was drafted that combined the MDD, the *Active Implantable Medical Devices Directive*, and the *In Vitro Diagnostic Regulations* into a single document that also included software and accessories in its definition of medical devices. The MDR was published in the *Official Journal of the European Union* in May 2017, and full implementation is expected to occur in 2020.

The key difference between the MDD and the MDR is the requirement for clinical evaluations. Equivalence will become an increasingly difficult means by which to demonstrate compliance, and Class III devices will be expected to do clinical evaluations. Strict rules for clinical investigations and alignment to Clinical Trials Regulations are introduced in Chapter VI, Articles 62 to 82 for the MDR.

MedDev 2.7/1 Revision 4 as a Pathway to MDR

MedDev 2.7/1 Revision 4 is a good first step for the transition to MDR, as it implements many of the changes in regards to establishing equivalence and collecting clinical data. It is also important to note that all devices approved under Revision 4 of the MDD that are lawfully already placed on the European market will be grandfathered in as in compliance with the MDR and will not have to perform clinical investigations to continue being sold on the European market. However, these products will have to update their clinical evaluation reports (CERs) to adhere to the new requirements of the MDR in all other ways.

So, let's first explore Revision 4 and how it differs from Revision 3 of MedDev 2.7/1. The first thing one notes is that it is significantly longer than Revision 3, being 65 pages instead of 46. Most of the increase is due to more detailed and expansive requirements for clinical data. It is the goal of Revision 4 is to clarify what is meant by evaluation of clinical data and to provide more detailed examples of where one should seek clinical data. It also provides templates for manufacturers to follow and provides guidelines for Notified Bodies.

Revision 4 places a lot of emphasis on conducting clinical evaluation throughout the life cycle of a medical device, including its design stage. The CER should be updated annually per Revision 4, which means all of the supporting reports that drive change must be updated annually as well. Specifically, the literature search results and the post-market surveillance (PMS) reports will need to be conducted annually. There is an expectation in Revision 4 that post market clinical follow-ups (PMCF) will also be conducted, but it is not stated that these follow-ups are required or that they must be done on an annual basis.

Revision 4 provides guidance on where and how to search for literature. It is necessary for the manufacturer to have a governing literature search protocol that is developed and approved by the manufacturer prior to conducting the literature search. This document must be cited in the CER. In addition, the full results of the literature searches must be kept in a file that is available for the Notified Body to review. It must show which articles were selected and which were rejected based on the criteria established in the protocol. There is further guidance on how to analyze each article found and what types of articles should be rejected.

It is still possible to use data from an equivalent device; however, the definition of "equivalence" has been narrowed and refined, especially as compared to the FDA's definition of "substantial equivalence." For Revision 4, the equivalent device must be the same geometry, material, and function as the manufacturer's device. If only two of the criteria are met, say function and geometry, but the material is a different chemical composition, then it will be difficult to use as equivalent. The evaluator would have to justify why the device could still be used. Thus, multiple literature searches will have to be performed to find equivalence for each feature of a device. It is further necessary to find pictures of the equivalent devices for each feature claimed as equivalent.

Revision 4 requires transparency from manufacturers on their methods used to gather data about their device. This means all data collected must be logged in raw form, and methods used to analyze the raw

data must be documented in a report. Thus, the CER will reference multiple supporting documents and will contain summarized tables and/or reports of the findings of the supporting documents.

Revision 4 makes compliance with the essential requirements for safety, performance, and risk-benefit analysis a priority. The new template provided for Revision 4 provides a separate subsection for each of these topics so that the manufacturer specially addresses each one.

There are also more detailed instructions on how to establish and document the state-of-the-art and available treatment options. The CER should include an introduction and background to the field in which the device is used, and therefore, a literature search specifically for finding this data will be necessary. The manufacturer will need to address the risk and benefits of the various treatment options available.

Revision 4 requires that the Notified Body challenge the manufacturer's claims of equivalence with other devices. The Notified Body will thus need access to all of the log data so they can review the assumptions and choices made by the evaluator. This is a significant deviation from Revision 3, but is a foreshadowing of things to come in MDR 2017/745, where the Notified Body's role changes from collaborator with the manufacturer to a policing force.

In Revision 4, the links between clinical evaluation, PMS, and PMCF reports are now the driving forces for the CER updates. It will therefore be critical for a PMS system to be established and reported upon annually at least two months prior to a CER update. The same is true for a PMCF system, although this could probably be most easily accomplished by gathering survey data from representatives present during the surgical procedure and recording it in a database.

There is now a specific requirement in Revision 4 for demonstrating the scientific validity of all data found, including statistical considerations. Percentages are no longer considered sufficient for analysis, so the data should be evaluated with statistics, such as mean, standard deviation, and P-value, when making claims about safety, performance, or risk-benefit of a medical device.

Finally, there are now specific requirements for the expertise and experience of CER authors and evaluators. Postgraduate education and 5 years of experience in the field or 10 years of experience in the field and justification of one's expertise are now required. In addition, each evaluator must make a Declaration of Interest, which discloses their affiliation with the manufacturer.

<u>Medical Device Regulation Preparations</u>

The most important take away for manufacturers to prepare for the MDR is that they need to define protocols for and start gathering clinical and market data now for all their medical devices, software, and accessories. These protocols are used to generate the literature search, clinical trial, PMS, and PMCF reports. Below is an outline of the key protocols which need to be written. Reports will then be generated annually based on these protocols, and the collective results will be used to drive the CER.

- **Literature search protocol** with weighting and selection criteria for articles, full database of raw results, and a literature search results report. These three items can be compiled into

one report with all the results attached, but it would make more sense to keep them separate, as the raw data and results report needs to be updated annually.

- **Post-market surveillance (PMS) report** that routinely monitors various other types of data, both internally and externally generated, such as incident reports, MAUDE, national joint registries, feedback from users, etc. for issues or problems with the Instructions for Use (IFUs), accessories, devices, or marketing materials associated with the product.
- **Post-market clinical follow-up (PMCF) report** that monitors performance and safety of the device in the surgical arena, such as incident reports, MAUDE, national joint registries, feedback from users, surveys completed by representatives in the operating room, etc. for issues or problems with the device's clinical performance.

The purpose of the CER then becomes a decision-making document. Based on what is found in the literature, PMS, and PMCF reports, what changes or improvements need to be made to the device? What plans will be implemented to make the needed changes if any are identified during the CER? If this is a new medical device, what was learned from the clinical trial about the device's performance?

All accessories used with or for a medical device, even if they have no intended medical purpose, are now considered medical devices. The definition of an accessory is expanded to "assist" a device to be used (before, the definition said "enable" a device to be used). Another significant increase of scope is that devices for cleaning, disinfecting, or sterilizing a device will also be classified as medical devices. Thus, it is Dr. Munro's interpretation that all surgical instruments and implant trials used during a surgical procedure would be classified as medical devices. The tray and the sterilization techniques for devices and instruments would be regulated by their manufacturer or operator, not Ortho Development, but the packaging and packaging systems would need to be monitored with a database maintained by the manufacturer. The Notified Body will be involved with regulating sterility of all packaging and packaging systems, too. If all surgical instruments and implant trials are going to be part of the CER, this will significantly increase the scope of the document.

<u>EUDAMED and UDI</u>

Additionally, each device will require a Unique Device Identification (UDI), and there will be a uniform, international database where the manufacturer will have to maintain their UDI information and cross reference it to its Declaration of Conformity. This database, called EUDAMED, will be accessible to various users, some of it even to the individual patient. EUDAMED must also be used to document PMCF studies. There remain open questions about how this will impact privacy laws and security concerns. EUDAMED will require Member States to issue unique Single Registration Numbers to each EUDAMED user. This is expected to be a complex and demanding effort for which no resources have been identified yet.

Manufacturers will be required to supply their Competent Authority will all information necessary to demonstrate conformity with the MDR, as well as share that information with patients or their representatives claiming compensation. An additional part of the requirement is the UDI and a new label of either "MD" for medical device and "IVD" for in vitro device.

Role of Notified Body

The role of the Notified Body is greatly changed with the MDR. The Notified Body is no longer an industry partner, but rather a police-like extension of the Competent Authority, which includes a requirement for unannounced inspections of manufacturers at least once every five years. The Notified Body will be mandated to test samples from the production and/or manufacturing process, and they are encouraged to analyze samples from the market. It is unclear who will pay for testing of these samples, although it seems likely that this expense will be passed on to manufacturers. It is expected that the number of Notified Bodies will significantly diminish with the expanded responsibilities mandated in Annex VII. The Notified Body must send its clinical evaluation assessment report to the relevant expert panel (Annex IX), and the expert panel has the option of issuing an opinion of the application within 60 days. After that, if no opinion has been issued, the Notified Body can certify the device. The expert panels are appointed by the EU Commission, and it is unclear how experts will be located. Costs related to these expert panels will likely be covered by fees paid by the manufacturer to the EU Commission. Like the expert panels, Notified Bodies are expected to see a shortage of personnel with competence to perform reviews and audits, which may lead to significant delays and higher costs for manufacturers.

Conclusions

Complying with MDR by 2020 is going to be a sizeable undertaking for most medical device manufacturers, so it is important to begin implementing a strategy now. Developing protocols for literature searches, clinical trials, post market surveillance, and post market clinical follow up are good first steps towards a plan. The next step will be to use each of these protocols to generate a set of initial reports, which will identify the potential gaps in compliance for that device. It is advisable to use MedDev 2.7/1 Revision 4 as a template and bridge, but the ultimate goal should be to comply with MDR—moving away from clinical literature and towards self-generated clinical data for assessing the performance of one's medical devices.

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MDR Preparation Timeline

With any multi-step undertaking, it's best to set deadlines to ensure that you stay on track to meet your final goal. MDR is no different. I suggest the following three steps and target timeframes to ensure that you're ready when MDR takes effect in 2020.

Now to February 2018: Establish protocols for literature reviews, clinical trials, postmarket surveillance and postmarket clinical follow-up. I suggest starting with a skeleton for each protocol with the key items that each should accomplish. Use these outlines to perform an initial literature search or postmarket

surveillance, for instance, to see how well it works. These trial runs will quickly identify where more work is needed.

February 2018 – Ongoing: Triage your medical device systems to determine which ones must comply with MDR first. Those that are due for renewal before 2020 will need to comply with MedDev 2.7/1 Revision 4; however, I would skip this and do the extra work to try to comply with MDR. Use the protocols developed for MDR compliance and implement them for Revision 4 CERs, testing how well they work. This will better distribute the work over the next two-and-a-half years and ease the transition process.

January – December 2018: Complete training of one or more individuals on EUDAMED. Start early, because the relabeling and UDI process will be lengthy and training will fill up as 2020 approaches. Having a UDI numbering system developed and a means of uploading the data required will be critical to your success with MDR.