mantrasystems

Mastering the MDR

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About the author and Mantra Systems Ltd

Mantra Systems Ltd delivers a completely new form of medical device regulatory support. Unlike any other consulting company, we have a team of specially-trained medical doctors who apply clinical acumen and industry expertise to your medical device compliance challenges. With the new MDR focusing heavily on clinical evidence, our knowledge will provide the support you need to ensure your devices meet the requirements of the MDR.

This White Paper is part of a series written by Dr Paul Hercock, the CEO & founder of Mantra Systems Ltd. Paul is dual-trained in medicine and law. He spent 14 years working for the NHS as a front-line clinician and then obtained a Graduate Diploma in Law with distinction from Nottingham Law School. While at law school, Paul established a medical device start-up. He then went on to specialise in providing medical and regulatory support to medical device companies including Johnson & Johnson and Bonesupport AB.

Leveraging Paul's expertise, Mantra Systems comprises an infrastructure of specially-trained medical doctors that apply their clinical knowledge to provide support services to medical device manufacturers working to achieve compliance of their medical devices with the MDR.

Don't allow the upcoming MDR implementation to adversely affect your business. This White Paper will enable you to develop a thorough understanding of the MDR as it applies to medical device manufacturers, forming the basis of your MDR compliance strategy.

Introduction

The purpose of this document is to summarise the MDR and make its contents easy to digest. It is intended to highlight those areas in the text that are most relevant to medical device manufacturers. It serves as a commentary on the MDR and does not constitute formal advice.

The medical device sector is one of the most tightly regulated market sectors in the world. All activities – from device conception and design, through realization, manufacture, device marketing and surveillance activities after release – are governed by legislation that outlines responsibilities for all players within the market. It is essential that all operatives within the medical device sector, especially medical device manufacturers, have a thorough understanding of this regulatory framework. As will be seen throughout this document, the Medical Device Regulation (MDR) is the central legislation that must be understood in detail in order to ensure regulatory compliance of medical devices.

On 26th May 2021 the Medical Device Regulations (EU) 2017/745 will formally replace the Medical Devices Directive 93/42/EEC (MDD) after a four-year transition period, extended by one year due to the COVID-19 crisis. The introduction of the Medical Device Regulation, commonly known as the MDR, sees the largest overhaul of medical device legislation in decades. From 26th May 2020, the MDR will be fully in force and all medical devices (and medical device economic players) in the European Union will be subject to it.

The MDD has been replaced because, although generally robust and relatively permissive of innovation, it was considered to have a number of flaws. Its limitations in enforcing medical device safety, reliability and general product quality were exposed by notorious incidents such as the metal-on-metal hip scandal. It was also insufficiently flexible to adequately regulate technological developments that have arisen since it was drafted, such as diagnostic software and nanomaterials. For these reasons and others, legislators were compelled to implement reform and the MDR was the result.

The MDR describes a detailed regulatory environment around medical device design, construction, manufacturing, marketing, surveillance, senescence and oversight. However, the MDR itself is 175 pages of legal text, making it a difficult and demanding instrument to work with directly. After reading this White Paper, you will understand the MDR in greater detail than ever before.

Page references for each Chapter/Annex relate to the pdf version of the full-text MDR. Article 2, containing useful definitions, starts on page 15 of the pdf.

MDR structure overview

The full text version of the MDR is 175 pages long. It begins with an untitled introductory section that places the new legislation in context and sets out the primary objectives and purposes behind the drafting and implementation of MDR.

The introduction outlines:

- The status pre-MDR
- The reasons for implementing new legislation, including the need to establish a more robust regulatory framework that ensures a high degree of safety while facilitating innovation
- The intentions of MDR, including:
    - Set high standards of quality and safety
    - Account for small and medium sized companies and their specific needs as well as those of large companies
    - Harmonise rules for medical device regulation across member states and globally
    - Ensure that data generated in clinical investigations relating to medical devices is reliable and robust, and that the safety of subjects is prioritised
    - Reinforce some existing rules on scrutiny of important entities such as Notified Bodies
    - Reinforce rules on clinical evaluation, vigilance and market surveillance
    - Harmonise legislation on medical devices and active implantable medical devices into one instrument, replacing two separate ones.

The introduction details what is and is not in scope of the MDR. Specifically, the legislation does NOT apply to in-vitro diagnostic medical devices, products containing viable cellular material, blood products, purely medicinal products (e.g. drugs), cosmetics, or food. MDR **does** apply to:

- Products that are a combination of devices and medicinal products, on a case-by-case basis
- Products made from non-viable tissue of human origin

- Some products that may claim a non-medical use but that are sufficiently similar to other medical devices in terms of function and any risks that they generate
- Software that is specifically designed for a medical purpose.

Expectations regarding economic players (companies active in the sector, whether manufacturers or providers of support services) are also detailed in the introduction. New specific requirements include that manufacturers must have sufficient financial coverage to cover any potential liability arising from sale or use of their devices.

The introduction outlines a new requirement for all medical devices (except those that are custom made) to use a Unique Device Identification (UDI) system to promote traceability of devices. For this and other reasons, the MDR sees the introduction of a centralised database to store and track information about devices in the market, along with data and investigations relating to them.

The introduction concludes with comments about increased scrutiny of Notified Bodies and emphasises the importance of every manufacturer having a comprehensive post-market surveillance (PMS) system and quality management system (QMS).

After the introduction, the MDR text moves on to the substantive sections that contain the "meat" of the legislation. This comprises the **Chapters** that each contain multiple related **Articles** outlining the law itself. The chapters are followed by a series of **Annexes** that detail specific procedures and requirements that are necessary in order to comply with the law contained within the Articles. In other words, very loosely, the Chapters can be thought of as stating "what to do", while the Annexes act as a binding guide as to "how to do it".

The **Chapters** most relevant to medical device manufacturers are:

- Chapter I: Scope and definitions
- Chapter II: Making available on the market, CE-Marking, economic operators
- Chapter III: Identification and traceability of devices
- Chapter V: Classification and conformity assessment
- Chapter VI: Clinical evaluation and clinical investigations
- Chapter VII: Post-market surveillance, vigilance and market surveillance

Other chapters detail requirements for Notified Bodies, data protection, and co-operation between member states.

The **Annexes** are generally highly informative and can serve as a sequence of checklists for

ensuring that the obligations imposed by the MDR have been met. In some cases, the Annexes list a useful sequence of steps to undertake in performing a task or preparing a document. Becoming familiar with the Annexes will render achieving MDR compliance much more attainable. The Annexes with most relevance to medical device manufacturers are:

- Annex I: General safety and performance requirements
- Annex II: Technical documentation
- Annex VIII: Classification rules
- Annex IX to XI: Conformity assessment routes
- Annex XIV: Clinical evaluation and PMCF
- Annex XV: Clinical investigation

Annex VIII works best when used as a flow-chart in determining the regulatory Class of each individual medical device. It is self-explanatory when used in this way, and for this reason is not included in this summary document. It can be found on page 140 of the full-text legislation.

Chapter I: Scope and definitions (MDR pg 13)

Article 1 details the subject matter and scope of the MDR as well as a timetable for its implementation. It repeats some of the material on scope that is covered in the introductory part of the MDR. It states that the MDR applies to:

- The placing on the market of medical devices for human use
- Clinical investigations concerning such devices
- The monitoring of medical devices on the market
- The activities of other economic operators such as Notified Bodies and competent authorities

Notified Bodies are specialist companies that are authorised to assess devices and their supporting documentation for compliance with the MDR. The award of a certificate of conformity from a Notified Body allows the manufacturer to affix a CE-mark to their device and market that device in the EU. An example of a Notified Body in the UK is BSI (www.bsigroup.com). Competent authorities are emanations of central government that oversee the medical device market within that country. In the UK the competent authority is the Medicines and Healthcare products Regulatory Agency (MHRA).

Article 1 goes into detail about the applicability of MDR to devices that have a medicinal product as an integral part (e.g. bone cements containing antibiotics), and to devices that are designed to administer a medicinal product (e.g. “Epipen” adrenaline syringes for anaphylaxis).

- If a device has a medicinal product as an integral part, it falls under MDR if the action of the medicinal product is ancillary to the action of the device
- If the device merely delivers a medicinal product without altering it, then it falls under MDR
- If the product is placed on the market in such a way that the combination forms a single integral product intended for use exclusively in the given combination, then it falls outside MDR and is subject to Directive 2001/83/EC or Regulation 726/2004.

Article 2 contains a very useful list of definitions that should be turned to whenever a technical term is encountered elsewhere in the MDR. As mentioned above, Article 2 begins on page 15 of the downloadable PDF version of the MDR.

Chapter II: Making available on the Market, CE-Marking, economic operators (MDR pg 21)

This is a comprehensive chapter concerning the placing of medical devices into the market. In order to be placed into the market, there must be some indication that a device complies with the requirements of MDR. There must also be at least one "economic operator" (such as a manufacturer). Therefore it makes sense that this chapter also covers CE-marking and requirements placed upon economic operators.

Article 5 begins by stating that a device may only be placed on the market if it complies with MDR when the device is "...supplied, properly installed, maintained and used in accordance with its intended purpose." It also states that all devices must meet the general safety and performance requirements (listed in Annex I and detailed later in this document) and must demonstrate this through a structured process of clinical evaluation.

Article 7 prohibits the use of text, names, images, etc, which may mislead the patient or user.

Article 8 moves the discussion onto the mechanics of placing a device on the market. It states that if a device/manufacturer is in conformity to a "harmonised standard" that is appropriate and relevant, it will be assumed to be compliant with the corresponding part of the MDR. Harmonised standards include, for example, the various ISO standards (www.iso.org/standards) that sit outside the MDR itself and are not legal instruments, but that are recognised internationally as standards within the industry. The ISO standards most relevant to most medical device manufacturers are ISO 13485, ISO 14971 and ISO 14155.

Article 9 concerns itself with situations where no such harmonised standard exists. In this situation, after taking expert advice, the EU Commission itself may adopt "Common Specifications" (or CS for short) that will serve a similar purpose to ISO standards and other harmonised standards. Again, conformity with a CS will lead to a presumption of conformity with the relevant part of MDR.

Article 10 is important because it outlines general requirements for device manufacturers themselves. Manufacturers must:

- Ensure that their medical devices are designed and made in accordance with MDR
- Have a risk management system in accordance with Section 3 Annex I of the MDR

- Conduct an appropriate clinical evaluation of all their devices
- Maintain a record of up to date technical documentation (detailed later)
- Have an implemented Quality Management System (QMS)

If MDR compliance has been demonstrated after a suitable assessment (involving a Notified Body in many cases), manufacturers must affix a CE-mark to their devices and must comply with requirements for using a Unique Device Identification (UDI) system. They must also ensure that procedures are in place to ensure that device production continues to be in conformity with MDR as production scales, with any procedural changes declared to regulators.

Article 10 provides some detail about requirements for the Quality Management System (QMS) that all manufacturers must:

- Establish
- Document
- Implement
- Maintain
- Keep up to date
- Continually improve.

The QMS must cover all parts of the manufacturer's organisation. It must include at least the following aspects, all of which are detailed elsewhere in the MDR and this document:

- A strategy for regulatory compliance
- Identification of applicable general safety and performance requirements (SPRs)
- Responsibility of management
- Resource management including management of subcontractors
- Risk management
- Clinical evaluation, including Post Market Clinical Follow-up (PMCF)
- Product realisation process
- Verification of UDI assignments

- Set-up and maintenance of post-market surveillance (PMS) system
- Procedure for communications with regulators such as competent authorities and notified bodies
- Process for reporting serious incidences
- Preventative And Corrective Action (PACA) management
- Processes for monitoring and measuring outputs of interventions

Article 10 concludes by making it clear that the manufacturer has primary responsibility for immediately correcting any non-conformities, including removing a product from the market if necessary. It also makes it clear that manufacturers must have financial coverage for any potential liability claims against them that may result from use of or contact with their devices.

Article 11 addresses the situation that arises when a medical device manufacturer is based outside the EU. In this case, they may only market their products inside the EU if they have an authorised representative (AR) company to represent them inside the union. Article 11 outlines a range of responsibilities for ARs, with the ultimate effect that ARs are jointly and severally liable with manufacturers for any device deficiencies.

Article 15 concludes the discussion on what is required of economic operators such as device manufacturers. It states that every manufacturer must have access to a person responsible for regulatory compliance and must allow them to undertake their duties without prejudice. Most companies will be required to employ their own such person; small manufacturers need not directly employ their own but must have one “permanently and continually” at their disposal. The person responsible for regulatory compliance must have either:

- Recognised qualification in law, medicine, pharmacy, engineering or other scientific discipline AND at least one year experience in regulatory affairs or medical device quality management
- OR a minimum of 4 years experience in regulatory affairs or medical device quality management.

If you do not have access to a suitably qualified person responsible for regulatory compliance, please email Mantra Systems at contact@mantrasystems.co.uk – our team of specially-trained medical doctors, through our unique framework, can help ensure that the requirement for "permanent and constant" availability is met.

Articles 19 and 20 detail the EU declaration of conformity and CE-marking. Medical device

manufacturers draw up an EU declaration of conformity when they believe that their obligations under MDR in respect of that product have been met. By drawing up such a declaration, the manufacturer assumes responsibility for MDR compliance, and will be held accountable if the declaration is later assessed as insufficiently evidenced. Article 20 simply states that CE-marks applied to products will conform to the general rules for the symbol itself.

Chapter III: Identification and traceability of devices (MDR pg 34)

The MDR imposes specific changes from the Medical Devices Directive (MDD) in terms of expectations for ensuring that individual medical devices can be identified and traced. MDR requires that:

- Every medical device has a unique device identification (UDI)
- Economic operators themselves must be easy to identify
- Economic operators must know which health institution or healthcare professional they have supplied a device to
- A central database must be established by the EU Commission (called “Eudamed”)
- A summary of safety and clinical performance of all Class III devices will be entered into the database.

Article 27 outlines what the UDI system aims to achieve and how the assignment of UDIs to devices will be coordinated. The UDI system is intended to permit the identification and traceability of medical devices so that, in the event of a query or problem, it can be known where they are in the market and who has been contacted by them. The detail of how the UDI system will function is contained within Annex VI (not summarised in this document). It is expected that manufacturers keep a record of the UDIs of their supplied devices; this is obligatory for manufacturers of class III devices.

Article 28 specifically calls for a centralised database, accessible to the public. Article 30 calls for economic operators themselves to be electronically registered on a central database, with Article 31 calling for a single registration number (SRN) to be supplied by the relevant Member State’s competent authority (MHRA in the UK).

Article 33 gives some details about Eudamed, the European database on medical devices. The Article outlines a system that goes beyond the simple identification and tracking of devices. It is intended to be a source of information available to the public and a way to ensure that national competent authorities remain up to date with developments. Eudamed will include:

- Registration of medical devices
- The UDI database

- Register of economic operators
- List of Notified Bodies and their certificates
- Electronic system on clinical investigations
- Electronic systems on vigilance and PMS
- Electronic system on market surveillance

Chapter V: Classification and conformity assessment (MDR pg 49)

Chapter V groups together Articles on the classification of devices with rules about performing conformity assessments on those devices. This makes sense because the rules for conformity assessment can differ depending on the class of the medical device in question.

Article 51 states that devices should be divided into Class I, IIa, IIb and III. Classification shall be undertaken according to rules specified in Annex VIII. Class I devices are the lowest risk, with perceived risk increasing progressively through Class IIa, IIb and finally Class III as the highest risk class. With higher risk comes a requirement for a more stringent conformity assessment procedure. Article 51 states that any dispute over device classification must be referred to the competent authority of the relevant member state for them to decide.

The detailed mechanics of performing conformity assessment procedures – assessing whether a device has met its MDR compliance obligations – is contained within Annexes IX to XI. Article 52 explains which Annex procedure to apply, depending upon the class of device and (to an extent) the preferred route of the manufacturer.

- Annex IX applies in its entirety to Class III devices, unless the manufacturer instead chooses to apply both Annex X and XI in their entirety.
- For Class IIb devices, Chapters I and III of Annex IX apply, unless the manufacturer chooses instead to apply Annexes X and XI in their entirety.
- For Class IIa devices, Chapters I and III of Annex IX apply unless the manufacturer instead chooses to submit technical documentation and devices for assessment under section 10 or 18 of Annex XI.
- For Class I devices, other than custom-made or investigational (e.g experimental) devices, manufacturers shall declare the conformity of their products by issuing the EU declaration of conformity referred to in Article 19 after drawing up the technical documentation as set out in Annexes II and III.
    - If Class I devices are intended to be sterile, have a measuring function, or are reusable surgical instruments, the manufacturer shall apply the procedures set out in Chapters I and III of Annex IX, or in Part A of Annex XI. However, the involvement of the notified body in those procedures shall be limited.

A Notified Body (NB) is an entity that has been accredited by a Member State to assess whether a product seeking to be placed on the market meets the requirements set out in

MDR. Article 53 governs the involvement of NBs in the conformity assessment procedure of medical devices. It states that manufacturers have a free choice of NB but that manufacturers must not lodge parallel applications with more than one NB for the same thing.

Article 56 contains rules for granting the EU certificate of conformity – the certificate issued by a NB if they find that a device submission complies with all relevant aspects of MDR. The certificate must be in an official EU language and must indicate a validity period (maximum 5 years). The certificate details must be entered into Eudamed. The NB must suspend or withdraw certification if it becomes aware of a reason why MDR requirements may no longer be met.

Article 59 contains an interesting exception. It states that, when in the public interest, a competent authority may authorize derogation from the standard conformity assessment procedure if it is deemed to be in the public interest. This would appear to allow emergency situations that may be difficult to predict in detail but which may require a degree of flexibility that is hard to find in the formal conformity assessment process.

Chapter VI: Clinical evaluation and clinical investigations (MDR pg 55)

This is a comprehensive chapter that details the rules for performing clinical evaluations and investigations into medical devices. It is important to remember that these terms have technical meanings in the context of MDR, defined in Article 2. The definitions contained in Article 2 are:

***Clinical Evaluation**: Systematic and planned process to generate continuously, collect, analyse and assess the clinical data of a medical device in order to verify safety and performance.*

***Clinical Investigation**: Any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a medical device.*

Therefore, a clinical investigation will normally be one component of a clinical evaluation. The output of the clinical evaluation process will be documented in a Clinical Evaluation Report (CER), an important part of the technical documentation that must be submitted towards a conformity assessment procedure in order for a device to achieve certification.

Under MDR the stated objectives of clinical evaluation are:

- To demonstrate conformity with the relevant general safety and performance requirements ("SPRs" – listed in Annex I)
- To evaluate the presence and rate of undesirable side-effects
- To determine the acceptability of the benefit-risk ratio of a device.

Article 61 allows the manufacturer to specify and justify the level of clinical evidence necessary to demonstrate conformity with the general SPRs. This makes sense – it would be impractical for the MDR to be prescriptive here, given the huge range of different devices available on the market. However, the apparent flexibility contained within Article 61 may also be a source of difficulty for manufacturers since they can be left unsure of how to proceed. It is important for manufacturers to take expert advice in this case. Regardless, all manufacturers must plan, conduct and document a clinical evaluation following the process detailed in Annex XIV.

Article 61 provides some allowances for applying the principle of equivalence. Equivalence is the process of 'pointing to' a device that already has regulatory approval and claiming that the device seeking approval is sufficiently similar to the approved one to be considered

equivalent from a regulatory perspective. Successfully claiming equivalence hugely reduces the regulatory burden required for obtaining a CE-mark. The ability to claim equivalence, however, has been much reduced under MDR compared with MDD. Nonetheless, Article 61 does state that equivalence may be claimed if:

- It can be demonstrated that the already-approved device is equivalent technically, biologically and clinically to the one seeking approval
- The literature on the already-approved device demonstrates compliance of the device seeking approval with the general SPRs
- There is a contract in place explicitly granting full access to the technical files of the already-approved device. This would appear challenging when in many cases the already-approved device will be manufactured by a direct competitor.
- The clinical evaluation of the already-approved device was conducted in accordance with MDR, not MDD.

In all practicality, then, despite apparent allowances in the text, the ability to claim equivalence under MDR has been much reduced when compared with the ability to claim equivalence under MDD. This is another source of difficulty for some manufacturers making the transition to MDR, since their previously successful reliance on equivalence may now be inadmissible.

With Class III devices, Article 61 states that clinical investigations are always required (i.e. clinical equivalence is invalid) unless the device is a modification of an equivalent device produced by the same manufacturer.

The Article concludes by stating that clinical evaluation and the documents that support it must be constantly updated throughout the lifecycle of the device. The clinical evaluation process, its results, and the clinical evidence derived from it (i.e. what was done, the results, and what these results tell us about the device) must be documented as a component of a Clinical Evaluation Report (CER).

The process of clinical evaluation under MDR, and of writing and updating Clinical Evaluation Reports (CERs) to the required standard, is technical and challenging. Making mistakes can prove very costly, financially and otherwise. **Contact Mantra Systems today on 0114 386 3349 (or email: contact@mantrasystems.co.uk) to speak with one of our specialist advisors. We will ensure that your clinical evaluation process is MDR compliant from inception to conclusion.**

Article 62 gives general requirements for clinical investigations intended to demonstrate MDR conformity of medical devices. The MDR details requirements for all aspects of clinical

investigation, specifically regarding how an investigation is:

- Designed
- Authorised
- Conducted
- Recorded
- Reported

Annex XV outlines a detailed process for performing clinical investigations (a "how to", where the Article provides a "what to"). Article 62 details when the MDR requirements for clinical investigation apply. It states that they apply when an investigation is intended to:

- Establish and verify that, under normal conditions of use, a device is suitable for its intended purpose
- Establish and verify the purported clinical benefits specified by the manufacturer
- Establish and verify clinical safety and risk acceptability under normal use

Note the emphasis on normal use. Clinical investigations that are too limited in their inclusion criteria could be at the risk of falling outside the scope of normal use if not well-designed. On the other hand, the importance under MDR of collecting **real world data** to produce **real world evidence** should be clear.

Mantra Systems are specialists at designing and implementing real world evidence generation systems.

Paragraph 4 of Article 62 lists some common-sense conditions that are necessary before a clinical investigation may be conducted. It is worth reading this part of the Article in detail (page 57 of the PDF version) but it is possible to condense the contents into the following principles:

- Get appropriate approvals first
- Treat subjects fairly, especially if they are vulnerable
- Obtain informed consent
- Ensure that anticipated benefits outweigh any risks for subjects
- Protect any data obtained during the investigation

- Don't induce participation through undue influence
- Minimise pain, discomfort or fear for participants

Having dealt with what clinical evaluation is, what it is for, when MDR applies to clinical investigations and rules for performing clinical investigations, the chapter then goes on to Article 63 which outlines specific requirements for obtaining informed consent. For anyone already familiar with the principles of obtaining informed consent there is really nothing new here. Essentially, the requirements are that information given to a subject shall:

- Be given by an appropriate person
- Enable the subject to understand the investigation, what it is for, and what it might mean for them
- Guarantee protection for the subject if they refuse or later withdraw consent
- Be comprehensive, clear and understandable
- Include, where available, the EU-wide clinical investigation identification number

Article 64 gives specific rules for conducting a clinical investigation on incapacitated subjects. Again, these provisions are mostly common sense that will be familiar to those knowledgeable about consent in general. In sum, the Article requires:

- Consideration of whether the subject expressed a view before they became incapacitated; if so, this must be honoured
- Consent must be obtained from the subject's legally designated representative
- Subject must be given any information that they may be able to understand
- Consideration as to whether it is necessary to include incapacitated subjects in the investigation at all. Could sufficient data be obtained solely from non-incapacitated subjects? Do the benefits of including incapacitated subjects outweigh the risks?
- That there are no inducements of the subject's legally designated representative.

Other vulnerable or special groups defined in this section of the MDR include minors and pregnant/breastfeeding women, addressed in Articles 65 and 66 respectively. The rules on minors are generally as for those regarding incapacitated subjects but with provisions that enforce the respecting of wishes of minors who are sufficiently mature to form an opinion. Minors should be involved in the consent process as allowed for by their state of maturity. For pregnant/breastfeeding women, the rules in Article 62 apply but there must also be the potential for direct benefit to the woman and baby that outweighs any risks of participation

in the study.

If you recall, a requirement in the Article 62 provisions on necessary conditions that must be met before initiating an investigation was that appropriate approval must be obtained. Well, Article 70 outlines how to apply for such approval, and Article 71 tells Member States how to assess such applications for approval. Applications must be submitted to the Member State through the Eudamed e-system discussed elsewhere. This will generate a unique study identification number. The application for approval must include documentation specified in Chapter II of Annex XV. The Member State then has 10 days to decide whether the application is in scope of the MDR, to reject it, or to request extra information. Ultimately the application will either be accepted or rejected; if accepted, the date on which acceptance is notified to the applicant is known as the Validation Date.

The Chapter concludes substantively with Article 80 that covers the reporting of adverse events (AEs) and serious adverse events (SAEs), as well as SAE near misses. All SAEs caused by the device and all SAE near misses must be reported to the Member State who will decide what action to take. Clinical investigations involving the device may be suspended, terminated, modified or allowed to proceed according to the Member State's assessment of the SAE or SAE near miss. Where more than one Member State is involved, one will act as coordinating State to lead the investigation and response.

Chapter VII: Post-Market Surveillance (PMS), Vigilance, and Market Surveillance (MDR pg 71)

This chapter concerns itself with the monitoring of the safety and performance of medical devices following their release onto the market. Post-Market Surveillance (PMS) and vigilance are activities performed by the manufacturer – PMS on a planned-implement-review-act basis, vigilance on an 'always open' reactive basis. Market Surveillance, on the other hand, is performed by the competent authorities to provide a 'top down' perspective on device performance.

A PMS system forms a key part of a manufacturer's Quality Management System (QMS). For every medical device, Article 83 requires the manufacturer to plan, establish, document, implement, maintain and update a PMS plan. In other words, the PMS system must be designed, prospectively implemented, and then updated according to a structured assessment of how well it is working.

The PMS system must gather, record and analyse relevant data on the safety and performance of the device throughout its entire lifetime. The PMS system must be built in such a way that it is suited to determining, implementing and monitoring any required Preventative and Corrective Actions (PACAs).

Article 83 goes on to list particular areas where data from PMS should "in particular" be used:

- To update the benefit-risk analysis
- To feed improvements to risk management
- To update device design, Instructions For Use (IFU) and device labels
- To update clinical evaluation
- To identify needs for PACAs or field safety corrective actions (FSCAs)

Naturally, the outputs of the PMS process will be used to update the technical documentation that relates to the device in question.

Article 84 simply states that the PMS system will be based on a documented PMS plan constructed around the requirements detailed in Annex III.

PMS reporting requirements differ according to the risk class of the device in question. For Class I devices, a PMS report must be prepared that summarises relevant results,

conclusions, and any PACAs, updated as necessary. For all other device risk classes, a Periodic Safety Update Report (PSUR) must be prepared for every device that forms part of the technical documentation for that device. The PSUR must contain:

- A summary of the results and conclusions from PMS
- A rationale for and description of any PACAs
- Conclusions of benefit-risk determination
- Main findings of Post-Market Clinical Follow-up (PMCF)
- Volume of sales, estimated use population, and usage frequency of device (e.g. sold 1000 units that have been used on 100,000 patients, with each device contacting a patient twice per day)
- For Class IIb and Class III devices the PSUR must be updated annually
- For Class IIa devices the PSUR must be updated at least once every two years

Article 87 moves away from PMS and addresses the topic of Vigilance. This mostly concerns serious incidents, field safety corrective actions (FSCAs), and the monitoring of trends. A distinction must be made between serious incidents and expected side-effects that are clearly documented in product information and technical documentation.

Serious incidents are unexpected or "new" and must be reported to the competent authority. Serious incidents are those that take or threaten life or limb, or those that leave long-lasting harm. Manufacturers must report serious incidents as soon as a causal relationship between the device and the incident has been identified, and certainly no later than 15 days after the incident. If there is a serious public health threat, a report must be made within 2 days. If a patient has died, a 10 day limit for reporting applies. It is acceptable to submit a partial report initially, pending an update later as further information is uncovered by an investigation.

Article 87 outlines requirements for a wider response to any serious incident involving a medical device. It places a degree of responsibility on the Member State itself to undertake measures such as a targeted information campaign to encourage doctors and patients to report suspected serious incidents to competent authorities. This may be useful for a manufacturer to know when dealing with the aftermath of a serious incident involving one of their devices.

If an incident is deemed by a manufacturer not to be serious, or it is deemed to be an established side-effect, then it must be captured as part of Trend Reporting (see below). An explanatory statement must be provided by the manufacturer to the competent authority as

to why the incident was not regarded as serious. Where established side-effects are clearly documented in a well drafted risk assessment, this is usually uncomplicated.

Article 88 deals with the topic of Trend Reporting. Manufacturers must monitor the rate of known side-effects and report any statistically significant increase in the frequency or severity of them or any other non-serious incidents resulting from use of the device. Manufacturers must specify how this determination has been made in the PMS plan.

If a serious incident occurs and/or a FSCA becomes necessary, manufacturers need to know how to proceed. This is described in Article 89. The process shall include:

- An investigation on the facts
- A risk assessment focused on the event
- Co-operation with notified body and competent authority
- Not making changes to or sampling any devices that are under investigation – they must be supplied for examination "as is".

A field safety corrective action (FSCA) is designed to prevent recurrence of a serious incident. If a FSCA becomes necessary, the manufacturer must bring it to the attention of users of the device through a Field Safety Notice (FSN) that must include:

- UDI of devices affected
- Manufacturer details
- Reasons for FSCA
- Details of risks to patients, users or others
- Actions to be taken.

Article 92 describes the e-system that must be set up by the EU Commission through which the above-mentioned reports should be submitted. It is not necessary to go into this Article in detail since it outlines a number of tasks and objectives for the Commission itself.

The final section of the Chapter concerns market surveillance. Market surveillance (Article 93) is an analysis of characteristics and performance of devices by Member State competent authorities (i.e. market surveillance is a top-down analysis). Manufacturers, when requested, will be required to make available any documents and information requested by the competent authority, as well as samples of devices or access to devices free of charge. If the competent authority finds that a device presents an unacceptable risk, the manufacturer will be required to take any necessary action and the competent authority may restrict the

making available of the device on the market (Article 95).

Overall, therefore, this Chapter details prospective, reactive and top-down approaches to device surveillance, and outlines how unacceptable medical device performance will be handled, reported and corrected.

Annex I: General Safety and Performance Requirements (MDR pg 94)

Annex I provides a comprehensive breakdown of all the general Safety and Performance Requirements (SPRs) that must be met, where relevant, by all medical devices regardless of class. It contains three chapters:

- General requirements
- Requirements regarding design and manufacture
- Requirements regarding information supplied with the device

General requirements

- The device shall achieve the performance intended by the manufacturer, be safe and effective, and any residual risks must be acceptable when weighed against benefits
- Risks must be reduced as far as possible
- A risk management system must be established, implemented, documented and maintained. Paragraph 3 of this section (page 94 of the PDF version of the MDR) contains a checklist that should be used as reference when designing a risk management system.
- The device should maintain intended characteristics and performance when subjected to stresses which can occur during normal conditions of use
- Device must be designed, manufactured and packaged so that it is not adversely affected during transport and storage.

Requirements regarding design and manufacture

This chapter contains a long checklist of considerations. They should be worked through systematically with each device to see which requirements will apply. To help you gain an understanding of the content of this section, we here list a summary of the domains covered. It contains some requirements in the following domains:

- Chemical, physical and biological properties
- Substances and particles (including wear debris)
- Infection and contamination

- Devices incorporating a medicinal product
- Devices incorporating materials of biological origin
- Construction of devices and interaction with their environment
- Devices with a diagnostic or measuring function
- Protection against radiation, whether intended or not
- Electronic programmable systems (including software that is a medical device in its own right under MDR)
- Active devices, and devices connected to them
- Particular requirements for active implantable devices
- Protection against mechanical and thermal risks
- Protection against risks posed to patient or user by devices supplying energy or substances
- Protection against risks posed by devices intended for use by lay persons

As can be seen, this Chapter contains a detailed list of requirements. It is important to go through the general SPRs and identify which requirements relate to a particular device. This information can be applied in two ways:

- If the device is in development, develop a plan for how these requirements will be met and evidenced
- If the device is already in market
    - What evidence is there that these requirements have been met?
    - What gaps are there and how can they be addressed?

Requirements regarding information supplied with the device

This chapter comprises a further checklist to work through. It contains specific requirements for the device labels, the instructions for use (IFU), and device packaging. As with the other sections, if it is approached as a checklist this chapter is very accessible.

Annex II: Technical documentation (MDR pg 108)

This Annex contains a list of technical documentation that is required for submission in support of a device in order to demonstrate conformity. As with Annex I, this Annex functions best as a 'ready-reckoner' that can be used to ensure that all important/relevant aspects have been covered. The specific requirements for technical documentation relating to PMS are covered separately in Annex III.

Technical documentation should include:

- Device description and specification, including any variants and accessories
- Complete set of labels, packaging labels and transport packaging
- Instructions for use
- Design and manufacturing information
- Demonstration of conformity with general safety and performance requirements (SPRs) in Annex I, including
    - A list of those that apply, and an explanation of why others don't
    - Methods used to demonstrate conformity with them
    - Any harmonised standard (ISO standards) or CSs applied
- Benefit-risk analysis and risk management
- Product verification and validation
    - Engineering and pre-release tests
    - Evaluation of published literature relating to the device
    - Software validation, as relevant
- Clinical Evaluation Report (CER)
- PMCF plan and PMCF evaluation report (as in Part B of Annex XIV, see below)
- Occasional further information depending on the device.

Drafting many of these technical documents requires the input of a suitably trained doctor, available through Mantra Systems. Contact our team today.

Annex III: Technical documentation on PMS (MDR pg 112)

This is a short Annex that outlines the elements required for technical documentation on Post-Market Surveillance (PMS) systems relating to the device.

Documents must include:

- PMS plan
- Periodic Safety Update Report (PSUR – Article 86)
- PMS surveillance report (Article 85)

The PMS plan needs to demonstrate adherence to the obligation in Article 83 to prospectively plan, establish, document and implement a PMS. The PMS plan needs to:

- Address the collection and use of available information from:
    - Serious incidents, PSURs, FSCAs
    - Records of non-serious incidences and side-effects
    - Trend reporting information
    - Specialist or technical literature
    - Databases and/or registers
    - Feedback and complaints
    - Public information about similar devices (e.g. newspaper reports)
- Contain the following aspects:
    - A documented process to collect information from the above sources
    - Methods to assess collected data
    - Indicators/thresholds/rationale used during risk analysis
    - Methods for collecting and investigating complaints
    - Methods for statistical analysis of trends
    - Methods for communicating with competent authorities, notified bodies and

others

- Methods for tracing devices
- PMCF plan

At Mantra Systems, we are experts at developing and writing PMS Plans, PMCF Plans, PSURs, PMS Surveillance Reports and associated documentation. Contact a member of our team today for a free consultation.

Annex IX: Conformity assessment based on QMS and assessment of technical documentation (MDR pg 146)

Annexes IX, X and XI show the conformity assessment procedures that Article 52 requires manufacturers to undertake before placing a device on the market. The rules dictating which Annex to apply were discussed in the section on Article 52 above.

Annex IX is one possible conformity assessment route. It contains three chapters:

- Chapter I: Quality Management System (QMS)
- Chapter II: Assessment of technical documentation
- Chapter III: Administration provisions.

Chapter I: Quality Management System

The MDR requires manufacturers to establish, document and implement a QMS. The MDR also calls for QMSs to be assessed, and this part of Annex IX outlines the procedure for performing such an assessment.

Firstly, the manufacturer must lodge an application to have its QMS assessed by a notified body. The application must contain:

- Information about the manufacturer
- Information about the medical device in question
- Detail of QMS in full
- Draft of EU declaration of conformity
- PMS/PMCF documentation
- Documentation describing the clinical evaluation plan

The implementation of the QMS must comply with the MDR. This Chapter of Annex IX contains a long list of requirements that must be met before a QMS will be considered compliant. However, it is clear from this section of Annex IX that conformity with a harmonised standard such as ISO 13485 will normally lead to a rebuttable presumption of MDR compliance. It should be remembered, however, that the latest version of ISO 13485 has yet to be updated to reflect all changes imposed by the MDR, so familiarity with the

MDR itself is also required.

Chapter II: Assessment of Technical Documentation

- Applies to Class III and some Class IIb devices
- Manufacturer must lodge application for assessment of technical documentation with Notified Body (NB)
- NB must examine application using appropriately trained and knowledgeable employees
- NB must review clinical evidence presented by the manufacturer in the CER and related clinical evaluation. If necessary, the NB must use external clinical experts with "direct and current" experience relating to the device or target clinical condition
- Claims of equivalence must be assessed for validity
- NB must document the outcome of the assessment in a clinical evaluation assessment report.

Chapter II of Annex IX also lists additional procedures for Class III and some IIb devices whereby the EU Commission itself has visibility (via an expert panel) on the technical documents relating to those devices. Other situations that call for extra precautions are detailed in Chapter II and include:

- Devices incorporating a medicinal substance
- Devices incorporating non-viable tissues or cells of human or animal origin (or their derivatives)

Chapter III: Administrative Provisions

Lists requirements for retention of documents, EU declaration of conformity and NB-issued decisions and reports.

Annex X: Conformity assessment based on type-examination (MDR pg 155)

This Annex is similar to Annex IX in many ways but without the section relating to QMS assessment. This Annex calls for assessment of technical documentation and a representative sample of the device.

As with Annex IX, the NB shall employ device reviewers with sufficient clinical expertise, external if necessary, to perform the assessment.

If harmonised standards such as ISO standards have not been employed, this Annex calls for the performance of physical or laboratory tests by the NB to verify that the solutions adopted by the manufacturer meet the general SPRs.

If the documents and device sample are found to conform with requirements, the NB shall issue an EU type-examination certificate. 'Type' in this context means the specific device that has been subject to examination. A minor variant (e.g. the same device functionally and in every other way except painted blue rather than yellow) may be considered part of the same 'type'.

Annex XI: Conformity assessment based on product conformity verification (MDR pg 157)

The objective of this assessment procedure is to ensure that a device conforms to the 'type' for which an EU type-examination certificate has been issued (in accordance with Annex X), and that it meets all relevant MDR provisions. Two procedures are available in Annex XI:

- Production quality assurance
- Product verification

Part A: Production Quality Assurance

The medical device manufacturer shall ensure that a QMS approved for the manufacture of medical devices is implemented. When the manufacturer believes it has met its quality obligations, it shall draw up an EU declaration of conformity (Annex IV).

The manufacturer shall lodge an application for the assessment of its QMS by a NB. The assessment will be similar in scope to that for assessment under Annex IX but the submission will also include a copy of the EU type-examination certificate produced under Annex X.

If the QMS ensures that devices conform both to the required standard under MDR and to the type described in the EU type-examination certificate, the NB shall issue an EU quality assurance certificate.

Part B: Product Verification

This Part calls for verification of conformity through examination of every individual manufactured device. Each device examined must conform to the type described in EU type-examination certificate, AND meet requirements in the MDR.

Under this Part every device will be examined individually. The manufacturer must institute and update a PMS plan, including a PMCF plan, as well as procedures for ensuring compliance with obligations on vigilance and PMS as in Chapter VII MDR described above.

After examination of each individual product, if it conforms to type and MDR requirements then NB shall affix their identification number to the product as an indication that the NB finds that the device conforms to requirements.

Annex XIV: Clinical Evaluation and Post-Market Clinical Follow-up (PMCF) (MDR pg 164)

This is a nice, straightforward Annex that contains extremely important information on how to perform a clinical evaluation and how to structure a PMCF system. PMCF has gained much greater importance under MDR compared with its status under MDD and manufacturers are advised to seek guidance in ensuring that their PMCF systems are sufficient to meet MDR requirements.

Part A: Clinical Evaluation

Manufacturers must establish and continuously update a clinical evaluation which shall include at least:

- A list of identified relevant general SPRs
- Specification of the intended device – its purpose, indications, contra-indications and intended clinical benefits
- Outline of methods for examining clinical safety
- Outline of parameters to be used to assess benefit-risk ratio
- Clinical development plan: show progression from pre-release tests to first-in-man studies to confirmatory investigations, to pivotal clinical investigations and PMCF.

Any relevant published data must be identified and any gaps in the clinical evidence portfolio must be identified after a systematic literature review. All data must be appraised according to its ability to establish safety and performance of the device (this requirement speaks to study quality, power and relevance).

Manufacturers must then generate any new or additional clinical data required to address any gaps through properly designed clinical investigations.

Manufacturers must perform an overall analysis to reach conclusions about the safety and performance of the device including its clinical benefits. Clinical evaluation must:

- Be thorough and objective
- Account for both favourable and unfavourable data

- Be proportionate and appropriate to the device and its risks

If equivalence is claimed, data must demonstrate equivalence in clinical, technical and biological domains.

The results of clinical evaluation, and the clinical evidence on which it is based, shall be documented in a Clinical Evaluation Report (CER). This shall support the assessment of device conformity.

Performing clinical evaluation and writing a CER is a highly technical task that draws upon clinical expertise and direct experience working with MDR medical device regulatory submissions. Having access to specially-trained medical expertise will greatly increase the likelihood that MDR requirements are met. Contact our expert team today to discuss your requirements.

Part B: Post Market Clinical Follow-up (PMCF)

PMCF is a continuous process that serves to update the clinical evaluation. It comprises the proactive collection and evaluation of clinical data from the use of CE-marked medical devices in humans according to intended use. In other words, PMCF is in most part real world evidence. PMCF data must confirm the safety and performance of the device throughout its entire lifetime.

PMCF must be performed in accordance with a method detailed in a PMCF plan. This plan must specify how it will:

- Confirm safety and performance of the device throughout its expected lifetime
- Identify previously unknown side-effects
- Monitor the rate and severity of known side-effects
- Identify and analyse any emergent risks
- Ensure continued benefit-risk acceptability
- Identify any systematic misuse or off-label use

PMCF plan must include at least:

- General methods to be applied, e.g. gathering clinical data, user feedback and/or literature searching

- Specific methods to be used, e.g. medical device product registry
- Rationale for chosen general and specific methods
- A reference to relevant parts of the CER that contain a summary of PMCF data, an appraisal of the PMCF system, and results of data analysis.
- Specific objectives addressed by PMCF
- Evaluation of clinical data from equivalent/similar devices
- Reference to any harmonised standards/CSs used
- Timescale of PMCF activities

Results of PMCF shall be analysed and documented in a PMCF report that will form part of the CER and technical documentation.

Careful consideration needs to be given to the structure of the PMCF system that will be implemented in relation to each device. Mantra Systems are experts in developing medical device product registries, a powerful and future-proof method of collecting PMCF data that complies fully with MDR requirements. Contact a member of our team today.

Annex XV: Clinical Investigations (MDR pg 167)

This Annex outlines the requirements for performing clinical investigations in accordance with MDR. Conformity to the requirements in this Annex will help to ensure that the results of clinical investigations will be admissible for assessments under MDR. Annex XV contains three chapters:

- General requirements
- Documentation regarding application for clinical investigation
- Other obligations of sponsor

General requirements

- Conduct clinical investigations in accordance with recognised ethical principles.
- Methods shall be
    - In line with standards in the field
    - Appropriate to the device
    - Documented in a Clinical Investigation Plan (CIP)
    - Designed to address all relevant device features
- End-points of the investigation shall address the intended purpose, clinical benefits, performance and safety of the device
- Investigators shall have access to technical and clinical data regarding the device

Documentation regarding application for clinical investigation

This section lists what must be included in an application to perform a clinical investigation, in each following documents. It can be used as a simple checklist to ensure that documents are appropriately structured. We will cover this in more detail in the in-person training.

- Investigator's Brochure (IB) – document for principal investigator outlining investigators responsibilities in conducting the study
- Clinical Investigation Plan (CIP) – study protocol
- Other information

Other obligations of sponsor

- Ensure that serious adverse events occurring during the clinical investigation will be reported to the sponsor by investigators in a timely manner
- Keep documents such as IB, CIP and others for at least 10 years after clinical investigation has ended; 15 years if implantable device
- Appoint independent monitor to oversee the conduct of the investigation and its accordance with CIP
- Prove that the investigation was conducted in accordance with requirements of good clinical practice
- Prepare a clinical investigation report containing:
    - Cover/introduction page with basic details about the device, the investigation, principal investigators, etc
    - Author of report and date
    - Investigational device description with clear description of defined intended purpose
    - Outline summary of CIP
    - Results
    - Summary of serious adverse events, adverse device events, deficiencies and any corrective actions
    - Discussion and overall conclusions covering:
        - Safety and performance results
        - Assessment of risks and benefits of device
        - Specific precautions for any patient sub-populations
        - Implications for investigational device
        - Limitations of the clinical investigation

Performing clinical investigations under the MDR requires significant clinical expertise, a deep understanding of the MDR and associated legislation, and significant experience working in clinical data generation. Contact a member of our expert team today to discuss your requirements.

Conclusion

This concludes our commentary on the content of the MDR. We hope that this document has served to make the MDR easier to work with as an instrument. Throughout the year we will be running a number of exclusive training sessions that will build upon this foundation and lead to a detailed understanding of all aspects of the MDR and how to work with it.

To see the full scope of training available at Mantra Systems, and to find out how to register for a place, please visit www.mantrasystems.co.uk/mdr-training for more details.

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