

# Clinical Requirements under EU MDR: Understanding the Changes

The European Medical Device Regulation 2017/745 (MDR) entered into force on 26 May 2017, bringing together requirements from the Medical Devices Directive (MDD, 93/42/EEC), Active Implantable Medical Devices Directive (AIMDD, 90/385/EEC) and a variety of European guidance documents into a single Regulation. Although the date of application (the date after which all new devices must be placed on the market under the MDR rather than MDD or AIMDD) has been delayed from 26 May 2020 to 26 May 2021, allowing a transition period of four years, delays to publication of key guidance has left some manufacturers unsure of the action they need to take to achieve compliance.

Although some manufacturers may have MDD or AIMDD certificates that are valid to 26 May 2024, certificates which expire between 26 May 2021 and 26 May 2024 cannot be renewed; a new application under MDR will be required. Given an ever-contracting runway, businesses which have not already done so must address regulatory compliance urgently. There are many new requirements in the MDR as compared to the MDD or AIMDD, including requirements for clinical evidence, which means that additional action will be required to ensure that legacy devices can stay on the market under MDR. With the aim of providing some clarity to manufacturers, this article outlines the principal clinical requirements impacting pharmaceutical companies involved with medical devices, and offers practical advice for meeting the new clinical requirements.

## How the EU MDR Affects Pharmaceutical Manufacturers

Although it is generally perceived that medical devices and pharmaceuticals are two separate worlds, there are some situations in which pharmaceutical manufacturers may be impacted by the MDR, for example where the pharmaceutical manufacturer:

- also manufactures medical devices, such as devices with ancillary medicinal

substances;

- partners with or supplies to companies that manufacture medical devices (e.g. devices incorporating ancillary medicinal substances or drug delivery devices);
- manufactures a drug that is sold pre-packaged in a delivery device (Amendment to Directive 2001/83/EC).

### Impact on Manufacturers of Medical Devices which Incorporate an Ancillary Medicinal Substance

As for MDD, medical devices incorporating an ancillary medicinal substance are Class III under the MDR. Article 61 introduces new requirements for Class III devices, including:

- premarket clinical investigations required, including for legacy MDD devices if they do not meet certain criteria, including having “sufficient clinical data” to demonstrate safety, performance and benefit-risk in relation to the state of the art;
- annual Periodic Safety Update Reports (Article 86), summarising results and conclusions arising from evaluation of post-market surveillance data, including a rationale and description of any corrective and preventive actions;
- Summary of Safety and Clinical Performance (SSCP, Article 32) which is a publicly available (via EUDAMED) document which describes the clinical evidence upon which product certification is based, including an evaluation of how this compares with other possible therapy options. This also includes information on safety and residual risks, a suggested user profile and suggested training for users.

The requirement for premarket clinical investigations for Class III devices potentially poses the greatest challenge to manufacturers of Class III devices. Although there are certain exemptions for legacy devices, each of these are contingent upon the device already having “sufficient clinical data” to demonstrate safety, performance and clinical benefit. There will be no grandfathering of legacy devices, even if they have been on the market for several

decades. In addition, there are restrictions on the use of equivalence data for Class III and implantable devices, including:

- Data from other manufacturers’ equivalent devices cannot be used unless there is a contract in place with the OEM allowing access to all clinical and technical documentation on an ongoing basis, and the other manufacturer is in possession of an MDR certificate for the devices (the latter point is ambiguous in the MDR, but has been clarified by Commission guidance);
- Data from the manufacturer’s own devices can only be used if they are considered design modifications of existing devices currently certified under the AIMDD, MDD or MDR.

In both cases, there must be “sufficient clinical data” for the claimed equivalents, and there must be a post-market clinical follow-up (PMCF) plan design to confirm these conclusions with data from the subject devices.

The MDR also places greater emphasis on concepts of scientific validity and statistical validation; this applies equally to the clinical evaluation as to the design of post-market surveillance activities, including PMCF. Although these requirements were not alien to the MDD and AIMDD, the progressive nature of medical device regulation in Europe (from effectively no regulation prior to the publication of the Directive, to increasing requirements over successive revisions and publication of new guidance) meant that these requirements were less likely to be applied to legacy devices which had been on the market a long time. Under MDR, it is clearer that legacy status in itself does not exempt the manufacturer from requirements for quality and quantity of clinical evidence. Although Commission guidance document MDCG 2020-6 allows that confirmation of conformity may be achieved for some lower risk legacy devices with limited direct clinical evidence, it highlights that these justifications are expected to be exceptional rather than routine.

### Impact on Manufacturers of Class III Implantable Devices and Certain Active Devices Intended to Administer or Remove Medicinal Substances

In addition to the above, there is a new clinical consultation procedure for Class III implantable devices and certain active devices intended to administer or remove medicinal substances (Article 54). With a few exceptions (MDR renewals, minor design modifications to existing MDR certified devices, and cases where a Common Specification has been published which directly addresses clinical requirements and with which the device complies), all such devices will be put through an additional central European consultation procedure. This is in addition to any consultations required for the medicinal part of the device.

After the notified body has confirmed the acceptability of the clinical evidence for these devices, they will send the manufacturer's clinical evaluation report (CER), their assessment of the CER, and the PMCF plan to the Commission. The Commission will then transmit this to a clinical expert group, which may, dependent on the risk and novelty of the device, make recommendations for limited certificate duration, changes to indications, warnings or other elements of information for use, changes to the SSCP, changes to the PMCF plan, etc. The maximum duration of this consultation period is 60 days.

### Amendment to Directive 2001/83/EC Relating to Medicinal Products for Human Use

Where a device includes an integral medicinal substance, and the action of the medicinal substance is principal and not ancillary to that of the device (e.g. implantable devices where the primary mode of action is due to an integral medicinal substance rather than due to the mechanical action of the device), the combination is regulated as a medicine and not as a device. Similarly, medicinal products which are placed on the market in a way that it forms part of a single integral product intended to administer the medicinal product (e.g. pre-loaded injector pens, pre-loaded inhalers), are also regulated as medicines.

Article 117 of the MDR includes an amendment to Directive 2001/83/EC with respect to these types of medicinal products:

- in cases where the device part of the product has been certified under



the MDR, the results of the notified body conformity assessment must be included in the marketing authorisation dossier;

- in cases where there is no MDR certificate for the device part of the product, the authority will require an opinion from a notified body designated under the MDR on conformity of the device part to the relevant general safety and performance requirements of Annex I of the MDR.

### Clinical Requirements under the EU Medical Device Regulation

#### Use of Post-market Clinical Follow-up in the Transition from MDD / AIMDD to MDR

One of the many drivers for the publication of the MDR was the perception that many devices were relying on chains of equivalence, which when followed to their origins, led to insufficient or non-existent clinical evidence. Although MedDev 12.2/2' (MDD guidance on requirements for PMCF) indicated that the notified body shall "verify that PMCF is conducted when clinical evaluation was based exclusively on clinical data from equivalent devices for initial conformity assessment and that PMCF addresses the residual risks identified for the equivalent devices", in practice many notified bodies either missed this requirement (and the use of the word "shall" in the guidance indicates that the Commission did indeed consider it a requirement), or put undue emphasis on the word "exclusively", interpreting it to mean that any amount of data on the subject device, no matter how small or lacking in

scientific validity, meant that no PMCF study would be required.

Although notified bodies have been under increasing pressure since the publication of MedDev 2.7/1 rev 4<sup>2</sup> (MDD guidance on clinical evaluation for medical devices), and subsequently the MDR, to ensure that manufacturers address such gaps, this conversion has not been complete and there are still some Class III and implantable devices on the market which are relying on equivalence routes which will not be accepted under the MDR.

Prior to the publication of MDCG 2020-6, the prevailing opinion of the Commission has been that manufacturers should use the transition period between MDD and MDR to gather "sufficient clinical evidence" on their own devices via MDD PMCF studies, emphasising that there will be no grandfathering of legacy devices. However, a lack of direction as to what "sufficient clinical evidence" meant caused confusion. Although MedDev 2.7/1 offered a definition ("Sufficient clinical evidence: an amount and quality of clinical evidence to guarantee the scientific validity of the conclusions."), there was no agreement with respect to how much evidence was required to guarantee scientific validity. Pragmatic considerations came into play as well: Article 61 implied that any Class III or implantable device would require a clinical investigation if it did not have "sufficient clinical data", even the sutures, staples, pins, dental braces etc. of Article 61(6b). "Do we really have to do a PMCF clinical study on polypropylene sutures that have been on the market for

decades, to keep it on the market under MDR?" manufacturers asked.

MDCG 2020-6 provides some options:

1. Undertake PMCF studies within the indications included under your MDD certification to address clinical evidence gaps
2. Narrow the indications for use to those for which there is sufficient clinical data
3. Remove device variants with insufficient clinical data
4. For very low-risk devices meeting the definition of WET (well established technology) of MDCG 2020-6, assemble all clinical and non-clinical evidence to demonstrate unambiguously that the devices are safe and perform as intended, and back this up with an appropriate PMCF study under MDR to confirm these conclusions.

### Post-market Clinical Follow-up under MDR

A PMCF Plan is required for all devices under MDR. This may not be immediately obvious, as Annex III of the MDR says that the post-market surveillance plan shall include "a PMCF plan as referred to in Part B of Annex XIV, or a justification as to why a PMCF is not applicable." This seems to state in black and white that sometimes PMCF is not applicable. There is also wording in the conformity Annexes which indicates that PMCF is not always required.

However, Annex XIV Part B provides a new definition of PMCF: "PMCF shall be understood to be a continuous process that updates the clinical evaluation" and MDCG 2020-7<sup>3</sup> (MDR guidance on PMCF) states: "A PMCF plan shall specify the methods and procedures set up by the manufacturer, to proactively collect and evaluate clinical data from the use in or on humans of a CE marked medical device, placed on the market or put into service within its intended purpose, as referred to in the relevant conformity assessment procedure."

Because the requirements for a PMCF Plan as described in Annex XIV Part B include many data collection activities that have not traditionally been considered PMCF, the current interpretation from Team NB and the Commission is that use of the word PMCF alone in Annex III refers to a PMCF study, whereas the PMCF Plan will include other forms of post-market data collection (such as literature review, user feedback

etc.), and may include a justification for "no PMCF study". MDCG 2020-7 is presented as a template for the PMCF Plan with embedded guidance.

A further consideration is that manufacturers must now register PMCF studies with Member States at least 30 days prior to their commencement, if the study would involve additional invasive or burdensome interventions than would be performed under normal conditions of use. It should also be noted that the definition of "normal conditions of use" may differ between Member States, increasing the likelihood that such registration may be necessary where a study is being carried out in more than one Member State. This registration would include all the relevant PMCF study documentation, including approval from the relevant national ethics committee(s). This could lead theoretically to studies being rejected by an ethics committee in cases where a notified body has made certification contingent upon the completion of the study in question. In such cases, the manufacturer should contact their notified body as soon as possible with respect to any changes to their PMCF plans.

### Additional Measures for Traceability, Transparency and Heightened Surveillance: Implant Cards, SSCPs, PSURs and EUDAMED

The MDR includes several new measures to improve traceability, transparency and surveillance. These include the introduction of EUDAMED, implant cards, summary of safety and clinical performance (SSCP) and periodic safety update report (PSUR).

EUDAMED is the IT system set up by the European Commission to manage information related to medical devices and *in vitro* diagnostics. Under the MDR and IVDR (*In Vitro* Diagnostics Regulation), it will be expanded to include registration of actors (manufacturers, authorised representatives, importers, etc.) and devices, information about notified bodies and certificates issued under the MDR and IVDR, clinical investigation and performance studies, vigilance and post-market surveillance and market surveillance. It will facilitate sharing of information between Member States and will have modules that are open to the public. The first module is due to go live in December 2020.

The implant cards were a requirement under MDD for some Member States, but this has been formalised under the MDR. The implant card is a physical document

that will include information about the device, such as details needed for traceability, warnings, precautions and other safety measures, and requirements regarding device lifetime and follow-up. In addition to providing key safety information (in language understandable to a lay person), traceability information is intended to make it easier for a patient to identify if their device has been the subject of a recall or other corrective action. It can also be used to enable patients to identify themselves in case of special requirements (e.g. bypassing body scanners during security checks at airports). Implant cards are required for all implantable devices except those listed in Article 18(3): sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors.

The summary of safety and clinical performance (SSCP)<sup>4</sup> is a new requirement for Class III and implantable devices (excluding custom-made and investigational devices). The SSCPs provide a description of the device (including any previous variants, accessories and other devices used in combination), its intended purpose including indications, contraindications and target populations, a description of possible diagnostic or therapeutic alternatives, and a summary of the clinical evidence demonstrating the clinical safety and performance of the device. It will also include a suggested profile and training for users and information on residual risks and undesirable side-effects.

Two versions of the SSCP may be required. A clinician version is required for all Class III and implantable devices. The intent is to increase transparency to the clinician regarding the clinical evidence used to demonstrate the safety and performance of the device, and any planned or ongoing PMCF studies. For all implantable devices requiring implant cards, and for Class III devices used directly by the patient, a patient-specific SSCP will also be required. This is a simplified version of the SSCP, provided in language understandable to a lay person. The intent is to empower the patient to make more informed decisions regarding the treatment options available to them. MDCG 2019-9<sup>5</sup> Summary of safety and clinical performance: A Guide for Manufacturers and Notified Bodies, provides guidance on drafting SSCPs which expands significantly on the basic elements listed in Article 32. SSCPs will be publicly available via EUDAMED. The manufacturer label or

instructions for use must also identify the location of the SSCP on EUDAMED.

Periodic safety update reports (PSUR<sup>6</sup>) are another new requirement under MDR, applicable to Class IIa, IIb and III devices. The PSUR is a regular update of the results and conclusions of the analysis of the post-market surveillance data, including any PMCF studies. Although the original idea was based on the PSURs used for pharmacovigilance, the MDR PSUR goes beyond vigilance, into analysis of PMCF outputs, literature data, and other sources of clinical safety and performance data, to reconfirm the benefit-risk conclusion of the device. It also provides information regarding sales volumes, usage demographics and usage frequency, and reports on any preventive or corrective actions associated with the devices. PSURs are required at least annually for Class III and IIb devices, and at least every two years for Class IIa devices. An updated guidance document on PSURs is not yet available at the time of writing.

### Achieving Compliance in Time

To start with, manufacturers must assess the clinical evidence available for the device, and determine if this is sufficient to demonstrate safety, performance and benefit-risk in light of the new MDR requirements and associated guidance. This assessment may lead to wider commercial decisions about device portfolios, as manufacturers may see opportunities for product rationalisation. Where certification under the MDR is desired, it is essential not only to have sufficient clinical evidence (for all device variants, combination, indications, patient populations, etc.), but also to present it in a clear and unambiguous manner. Lack of clarity regarding clinical evidence will lead to delays and requests for further evidence from the notified body, which can be significantly more costly in terms of potential delays to market access than the cost of preparing complete and compliant documentation.

As noted earlier, manufacturers may be uncertain on what is meant by 'sufficient' evidence. For further clarity, it will be invaluable to seek support from experienced regulatory partners who have built up a strong understanding of the requirements. With limited time remaining until the EU MDR date of application in May 2021 and the last MDD / AIMDD certificates expiring in May 2024, industry experts can help to speed up the compliance



process by formulating a strategy, identifying gaps in data or documentation, providing specialist medical writing skills, and maintaining the entire life-cycle of clinical data now required for regulatory compliance. This may be particularly beneficial for biopharmaceutical, biologic and pharmaceutical companies who may not have prior experience with medical device regulation. Reviewing clinical data for medical devices is a matter of commercial urgency so manufacturers must not be complacent about the consequences of non-compliance, and look to finalise their EU MDR submissions as soon as possible.

### REFERENCES

1. MedDev 2.12/2 rev 2 Post Market Clinical Follow-Up Studies: A Guide for Manufacturers and Notified Bodies
2. MedDev 2.7/1 rev 4 Clinical Evaluation: A Guide for Manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC
3. Medical Device Coordination Group Document, MDCG 2020-7 Post-market clinical follow-up (PMCF) Plan Template: A guide for manufacturers and notified bodies, April 2020 [https://ec.europa.eu/health/sites/health/files/md\\_sector/docs/md\\_mdcg\\_2020\\_7\\_guidance\\_pmcf\\_plan\\_template\\_en.pdf](https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020_7_guidance_pmcf_plan_template_en.pdf)
4. See Article 32 of the EU Medical Device Regulation
5. Medical Device Coordination Group Document, Summary of safety and clinical performance: A

guide for manufacturers and notified bodies, August 2019 <https://ec.europa.eu/docsroom/documents/37323>

6. See Article 86 of the EU MDR



**Dr. Amie Smirthwaite**

A clinical and regulatory affairs expert, Dr. Amie Smirthwaite has over 25 years' postdoctoral experience in medical devices, spanning new product development, quality and regulatory systems, and clinical data evaluation. She is leading Maetrics' global clinical practice and brings a wealth of knowledge and experience, having worked for medical device companies, academic institutions and notified bodies. Prior to joining Maetrics, Amie was the Global Head of Clinical Compliance at BSI, having been with the organisation for 12 years. Amie developed BSI's clinical compliance team in response to requirements for Commission Implementing Regulation 2013/920 and EU Medical Device Regulation.