Leveraging Post-Market Surveillance and Post-Market Clinical Follow-Up Data to Support EU Medical Device Regulation (MDR) Compliance

Adrian Keene
Director of Product Development Strategy, NAMSA
Post-Market Surveillance (PMS) and Post-Market Clinical Follow-Up (PMCF) activities have been an important part of conformity to the European Union’s (EU) Medical Device Directive 93/42 EEC (MDD) and Active Implantable Device Directive 90/385/EEC (AIMD). In this White Paper, we will explain the increased emphasis on PMS and PMCF data under the new EU Medical Device Regulation 2017/745 (MDR), and provide a deeper understanding of how leveraging this data can support compliance with the regulation by the mandatory enforcement date of 26 May 2020.

Table of Contents

PMS and PMCF Background 4
PMS and PMCF Defined Within the MDD/AIMD and MDR 6
PMCF Defined 7
PMS Defined 8
Other PMS Associated Changes with Significant Impact 9
Preparing for MDR Implementation with Regards to PMS and PMCF 10
Reinforcing PMS Procedures and Data 15
PMCF Study Considerations 15
PMS Data Considerations 15
PMCF Data Considerations 16
The Benefits of MDR Preparation 16
Managing Notified Body Relationships 17
Conclusion 18
References 19
About the Author

Adrian Keene
Director of Product Development Strategy, NAMSA

Mr. Keene currently serves as the Director of Product Development Strategy at NAMSA. In this position, he utilizes his broad experience of effectively managing European medical device regulatory requirements to support clients worldwide, and to provide a balanced interpretation of the needs and expectations of competent authorities and manufacturers. Adrian previously held the position of Notified Body Head of SGS (UK), and also served as the Global Clinical Affairs and Regulatory Manager for Medical Devices (SGS) with responsibility for conformity assessment activities for high-risk (class III) devices under the Medical Devices Directive (MDD).

In all, Adrian has 25 years’ experience in the medical device industry with a wide array of medical products, including drug/device combination devices. He attended the School of Pharmacy at the University of London where he conducted postgraduate research in “Retinoid-Induced Skeletal Toxicity.” Mr. Keene also holds a diploma in “Managing Medical Product Innovation” from the Scandinavian International Management Institute.
PMS and PMCF Background

Although assessment of experience gained from devices in the “post-production phase” has been a requirement of the MDD and AIMD directives since their inception, the importance of both PMS and PMCF were emphasised in the 2007/47/EC amendment that entered into force 21 March 2010. That amendment included the following requirement in Annex X:

1.1c the clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.

However, there continues to be confusion within the medical device industry regarding the expectations of PMS and PMCF under the existing directives. While the new MDR provides further clarity, the goal posts have moved slightly.

The new MDR, which entered into force 26 May 2017, builds on the framework of the existing MDD and AIMD directives, but brings a number of new hurdles. Current major concerns include:

1. All stakeholders are embarked on “a voyage of discovery” regarding how the MDR will be implemented. Considerable work is still to be done by the EU Commission and Competent Authorities on the interpretation of the regulation, and how Notified Bodies (NB) will enforce requirements and ensure consistency is maintained across all NBs designated under the new regulation. The new MDR becomes fully applicable on 26 May 2020, yet current expectations are that NBs will only become designated to issue CE certification under the MDR in early/mid-2019. Thus, there is very little transition time for manufacturers. It remains unclear the approach NBs will take transitioning their clients to the MDR, for example how they will sample technical documentation for devices.

2. Although the Competent Authorities for Medical Devices (CAMD) have published their roadmap and FAQ documents, the urgency for publication of the practical guidance documents to facilitate manufacturers implementing the MDR cannot be overstated. Similarly, the Medical Device Co-ordination Group (MDCG) has been formed and has started to issue some documents, although they have a large “to do” list. As of May 2018, only one of the many implementing/delegating acts required has been published by the EU Commission.
3. There are recognized shortfalls in resources at all levels within the medical device sector to implement the regulation – whether it is the EU Commission or Competent Authorities setting the framework; NBs auditing and reviewing technical documentation or manufacturers ensuring that their products are compliant with the new requirements.

4. Due to the Technical File sampling regime under the MDD, some Technical Files may not have been reviewed by NBs. Furthermore, following the impact of the joint audit approach under 920/2013 and the requirements of MEDDEV 2.7.1 rev 4, the current expectations of a NB’s review may result in products previously considered compliant with the MDD to be noncompliant with the requirements of the new MDR.

There remains much uncertainty as to how the requirements of the MDR will be implemented, but one of the biggest issues for manufacturers is the lack of grandfathering of product conformity, i.e. **all products will need to demonstrate they comply with the new regulation** (although there is a significant period where existing certificates remain valid), even if manufacturers were already considered in compliance with current directives.

**With the significant risk of products being removed from the EU market due to loss of CE certification, there is an urgent need for manufacturers to first ensure that existing PMS processes and outputs are robust. Second, planning and implementing of PMCF activities to fill any gaps and support maintenance on the EU market is required, and may reinforce medical device clinical data to support ongoing CE re-certification upon MDR implementation.**

**Figure 1** shows the increased emphasis on PMS and PMCF within the new EU MDR.

**Figure 2** shows the scale of the challenge for MDR device certification based on estimated numbers of devices.

<table>
<thead>
<tr>
<th>Mentions within Regulatory Documents</th>
<th>Medical Device Directive 93/42/EEC</th>
<th>Medical Device Regulation 2017/745</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Market Surveillance (PMS)</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>Post-Market Clinical Follow-Up (PMCF)</td>
<td>3</td>
<td>57</td>
</tr>
</tbody>
</table>

**Figure 1:** Mentions of PMS and PMCF: MDD vs. MDR

<table>
<thead>
<tr>
<th>Number of Devices in the EU: 500,000+</th>
<th>Class I</th>
<th>Class IIa</th>
<th>Class IIb</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-205,000</td>
<td>-155,000</td>
<td>-90,000</td>
<td>-50,000</td>
</tr>
</tbody>
</table>

**Figure 2:** Estimated Number of Devices, by Class, in the EU
PMS and PMCF Defined within the MDD/AIMD and MDR

Current Situation

The MDD and AIMD have few clear precise definitions, with the EU Commission guidance documents (MEDDEVs) substantiating the principles laid down in the directives. Currently, there are three critical documents to be considered by global device manufacturers:

- MEDDEV 2.12/1 rev. 8 Guidelines on a medical devices vigilance system
- MEDDEV 2.7.1 rev. 4 Clinical Evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC
- MEDDEV 2.12-2 rev. 2 Guidelines on post-market clinical follow-up studies: a guide for manufacturers and notified bodies

As the requirements for vigilance are generally well understood, this document focuses on other aspects of PMS.

The current expectations under the existing directives for PMS and PMCF are detailed in Figure 3, with the position under the MDR shown in Figure 4 below. It is clear that the changes are evolutionary rather than revolutionary, but their impact is significant.

---

**PMS and PMCF Defined within the MDD/AIMD and MDR**

**Figure 3**: Expectations of PMS/PMCF under MDD.

---

**POST-MARKET SURVEILLANCE (PMS)**

**VIGILANCE (MEDDEV 2.12.1 REV. 8)**

- Customer complaints and warranty claims
- User feedback other than complaints, either directed to manufacturer or via sales force
- The media
- Other bodies (CA/MS)
- Maintenance/service reports
- Experience with similar devices made by the same or different manufacturer

**POST-MARKET CLINICAL FOLLOW-UP (MEDDEV 2.12 REV. 2)**

**PMCF STUDY:**

- The extended follow-up of patients enrolled in pre-market investigation
- A new clinical investigation (within scope of CE mark)
- A review of data from a device registry
- A review of relevant retrospective data from patients previously exposed to the device
- Any specific action/study intended to address a residual risk post-CE marking; this action is designed to answer a specific outstanding question
PMS and PMCF Defined within the MDD/AIMD and MDR

It is important to understand the definitions under the existing directives (as per MEDDEV 2.7.1 rev. 4), highlighting that robust PMS and PMCF are not a new requirement exclusive to the MDR.

**PMCF Defined**

**PMCF Plan:** The documented, proactive, organised methods and procedures set up by the manufacturer to collect clinical data based on the use of a CE-marked device corresponding to a particular design dossier or on the use of a group of medical devices belonging to the same subcategory or generic device group as defined in Directive 93/42/EEC. The objective is to confirm clinical performance and safety throughout the expected lifetime of the medical device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence. [MEDDEV 2.12/2 rev.2]

**PMCF Study:** A study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labelling. [MEDDEV 2.12/2 rev.2]

---

**Figure 4:** Expectations of PMS/PMCF under MDD

<table>
<thead>
<tr>
<th>VIGILANCE ACTIVITIES</th>
<th>PMS ACTIVITIES e.g.</th>
<th>PMCF ACTIVITIES e.g.</th>
<th>PMCF STUDY e.g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Management of incidences leading to death or serious deterioration in state of health</td>
<td>• Customer complaints and warranty claims</td>
<td>• Focus groups</td>
<td>• The extended follow-up of patients enrolled in pre-market investigation</td>
</tr>
<tr>
<td>• Trend reporting (Art 88)</td>
<td>• User feedback other than complaints, either directed to manufacturer or via sales force</td>
<td>• Customer surveys</td>
<td>• A new clinical investigation (within scope of CE mark)</td>
</tr>
<tr>
<td>• Analysis of serious incidents and field safety corrective actions (Art 89)</td>
<td>• The media</td>
<td>• Literature reviews</td>
<td>• A review of data from a device registry</td>
</tr>
<tr>
<td>• EUDAMED (Art 92)</td>
<td>• Other bodies (CA/MS)</td>
<td>• Device tracking/implant registries</td>
<td>• A review of relevant retrospective data from patients previously exposed to the device</td>
</tr>
<tr>
<td></td>
<td>• Maintenance/service reports</td>
<td>• User reaction during training programs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Experience with similar devices made by the same or different manufacturer</td>
<td>• In-house testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Retrieval studies on explants or trade-ins</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fracture analysis</td>
<td></td>
</tr>
</tbody>
</table>

**PERIODIC SAFETY UPDATE REPORT “PSUR” ART 86**

**SUMMARY OF SAFETY AND CLINICAL PERFORMANCE “SSCP” ART 32**
PMS Defined

Perhaps because PMS is a rather all-encompassing area, there has been a historical avoidance in clearly defining the scope. However, PMS can be considered an activity that collects any and all information that can be gathered in the post-production phase, which may come from numerous sources. MEDDEV 2.7.1 rev.4 does provide some guidance by referring to “PMS aspects that need regular updating in the clinical evaluation report:”

- new clinical data available for the device under evaluation
- new clinical data available for the equivalent device (if equivalence is claimed)
- new knowledge about known and potential hazards, risks, performance, benefits and claims, including:
  - data on clinical hazards seen in other products (hazard due to substances and technologies)
  - changes concerning current knowledge/ the state of the art, such as changes to applicable standards and guidance documents, new information relating to the medical condition managed with the device and its natural course, medical alternatives available to the target population
  - other aspects identified during PMS

The MDR helpfully offers more clarity regarding PMS and PMCF activities by providing the following definitions:

PMS per MDR

Chapter I Scope and definitions Article 1 (60): ‘post-market surveillance’ means all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions:

PMCF per MDR

Annex XIV Part B Post-Market Clinical Follow-Up (5):

PMCF shall be understood to be a continuous process that updates the clinical evaluation referred to in Article 61 and Part A of this Annex and shall be addressed in the manufacturer’s post-market surveillance
plan. When conducting PMCF, the manufacturer shall proactively collect and evaluate clinical data from the use in or on humans of a device which bears the CE marking and is placed on the market or put into service within its intended purpose as referred to in the relevant conformity assessment procedure, with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks on the basis of factual evidence.

The definitions in the MDR further clarify that PMCF is part of PMS, and although the majority of the scope of PMCF remains unchanged compared to MEDDEV 2.12-2, there is a broadening compared to the existing paradigm; it now includes the identification of possible systemic misuse or off label use of devices, to ensure the intended purpose as the device is indicated/promoted is correct.

It may also appear a semantic point, but the content of the PMCF plan described in the MDR now includes “gathering clinical experience gained, feedback from users, screening of scientific literature and of other sources of clinical data” which suggests that almost all devices are likely to require ongoing PMCF, rather than the historical position of the 93/42/EEC that “[if] PMCF is not deemed necessary, this must be duly justified and documented.” While all device manufacturers were previously required to appropriately justify either performing or not performing PMCF for the device in question, in practice PMCF was primarily conducted for high-risk devices (class III and implantable devices) and novel devices of lower classification.

It is now hard to imagine a circumstance for even a low-risk device with a long history of safe and effective clinical use where the manufacturer should not be gathering feedback from users and screening scientific literature and other sources of clinical data, and thus be performing some form of “PMCF” as defined by the MDR. However, it is important that in such a case that the PMCF activity is proportionate to risk, so although it is an additional activity, it should not be too onerous.

While there remains significant uncertainty about the MDR with many implementing and delegating acts to be drafted and approved, in the case of clinical evidence, MEDDEV 2.7.1 rev. 4 provides clear expectations for compliance with Annex X of the MDD and Annex 7 of the AIMD, as well as Annex XIV of the MDR. MEDDEV 2.7.1 rev. 4 emphasises the need to maintain clinical data throughout the product lifecycle, and the role PMS plays in maintaining evidence of compliance with essential requirements. It is recognized that many of the expectations of MEDDEV 2.7.1 rev. 4 were incorporated into the MDR (or the MEDDEV was written with the MDR in mind). The UK Competent Authority Medicines and Healthcare Products Regulatory Agency (MHRA) has indicated to manufacturers working on MDR implementation that “the best advice is to apply what you can now, to look to the MEDDEV 2.7/1 rev. 4 document for guidance, which is the state of the art ahead of the Regulations,” so if manufacturers meet the expectations of MEDDEV 2.7/1 rev. 4, they can have some confidence of compliance with MDR expectations.

Other PMS Associated Changes with Significant Impact

Compared to the MDD and AIMD, the MDR shows far greater emphasis on the complete product lifecycle with the need for continued updating of information based on active surveillance post-production. As MEDDEV 2.7.1 rev. 4 emphasized, the clinical evaluation is an ongoing process conducted throughout the lifecycle of a medical device, and continuous input into the process by PMS is critical to maintaining compliance to the
MDR. Article 86 of MDR formalises this with the output of PMS submitted into the Periodic Safety Update Report (PSUR) and the annual (class III and IIb) or biannual (class IIa) required updates; furthermore, the PSUR for class III and implantable devices will need to be submitted for NB review. Similarly, Article 85 details the requirement for a “Post-Market Surveillance Report” (PMSR) for class I devices. This additional activity will significantly impact both manufacturers and NBs, and it is expected that guidance documents yet to be issued will provide the further detail on the expected templates/content and submission/review processes.

The PSUR and PMSR are critical documents within the product technical documentation on post-market surveillance described in Annex III of the MDR, and are the outputs of the PMS processes which also need to be detailed within that technical documentation.

As well as the PSUR requirement, the addition of the “Summary of Safety and Clinical Performance,” or SSCP document (Article 32) for implantable and class III devices, will further increase demand on scarce resources. Similarly to the PSUR, implementing acts or guidance documents will provide the further detail on the expected templates/content and submission/review processes.

Preparing for MDR Implementation with Regards to PMS and PMCF

It is an unfortunate fact that previous CE certification, which was based on equivalency that occurred historically, may not meet the current expectations of clinical data under MEDDEV 2.7.1 rev. 4. Although the equivalency model has existed since at least 2003, the depth of assessment and expectations of NBs have varied considerably with the equivalence route to conformity being one of the significant concerns for stakeholders. The MDR substantially tightens the requirements for equivalence justification compared even to MEDDEV 2.7.1 rev. 4, with the requirement in Article 61 (5) that where the equivalence route is utilised for implantable and class III devices:

- the two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis; and
- the original clinical evaluation has been performed in compliance with the requirements of this Regulation; and
- the manufacturer of the second device provides clear evidence thereof to the notified body.

These requirements will prevent manufacturers of high risk devices from leveraging competitor data to minimize the scale and/or to avoid clinical investigations in their entirety when launching a “me too” product.

Note: Current interpretation of the MDR suggests this requirement only applies to implantable and class III devices, but future guidance from the CAMD Executive Group will hopefully clarify the position.

Similarly, clinical investigations previously performed may not meet the current expectations of ISO 14155, or Good Clinical Practice (GCP), which may compromise the quality of the clinical data upon which original CE certification was based.
Preparing for MDR Implementation with Regards to PMS and PMCF

Both of these issues may compromise the ability to meet the current expectations of MEDDEV 2.7.1 rev. 4, and thus the MDR.

Article 61 of the MDR details the circumstances where class III and implantable devices that are already CE certified will not require a further clinical investigation:

Article 61 (6)

The requirement to perform clinical investigations pursuant to paragraph 4 shall not apply to implantable devices and class III devices:

(a) which have been lawfully placed on the market or put into service in accordance with Directive 90/385/EEC or Directive 93/42/EEC and for which the clinical evaluation:

- is based on sufficient clinical data; and
- is in compliance with the relevant product-specific CS for the clinical evaluation of that kind of device, where such a CS is available; or

(b) that are sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors for which the clinical evaluation is based on sufficient clinical data and is in compliance with the relevant product-specific CS, where such a CS is available.

This begs the question “what is sufficient clinical data?” While the answer will always be a device-specific response with the clinical data demonstrating that the ERs/GSPRs are adequately addressed, the route to drawing that conclusion is via MEDDEV 2.7.1 rev. 4.

Note: While Article 61 (6) refers only to class III and implantable devices, the principles apply to all device classes; if a manufacturer lacks sufficient evidence to meet GSPR requirements, then how can CE certification be maintained?

The first step in any assessment is for a manufacturer to make a candid gap analysis of the clinical data, particularly if equivalence has previously been used to meet ER 6a. **This gap analysis should identify if all claims (safety, performance, technical and marketing) are adequately supported or identify the gaps that need to be addressed to support compliance with the new GSPR “general safety and performance requirements”** (formerly known as essential requirements under the MDD and AIMD).

Article 7 of EU MDR details the expectations of manufacturers when making claims, and the term “intended use/purpose” or “claims” may be used synonymously; Article 2(12), however, notes that the intended purpose is not limited to the label or instructions for use, but also promotional or sales materials, as well as statements specified in the clinical evaluation. Therefore, when reviewing claims, sales and promotional literature must also be included in addition to “regulatory” documentation such as the Clinical Evaluation Report (CER) (see Figure 5).
It is important to note that all is not lost if a determination concludes the equivalence justification is inadequate to meet current expectations, as we should remind ourselves why the equivalence route exists in the first place. The MEDDEVs are written in such a manner to allow, where applicable, a flexible approach which is proportionate to risk, avoiding unnecessary burdens to manufacturers, such as what previously may have been considered unwarranted clinical investigations. The equivalence route allows manufacturers to leverage other medical device clinical data in support of their own indications to achieve CE marking. However, most importantly, once a device is CE marked, that device will immediately generate its own clinical data via PMS and PMCF. The criticality of equivalence lessens as much more clinical data on the device itself is generated, but this presupposes that the PMS and PMCF activities are appropriately robust. Clinical data from use of devices in real-world settings should provide ongoing evidence of complying with regulatory requirements, and also provide the opportunity for better understanding of device performance and risks.

Manufacturers should also recognize the limitations of reactive PMS (rather than PMCF); these are detailed in MEDDEV 2.7.1 rev. 4, Annex A 7.2.d. i.e.:

PMS reports are compiled by the manufacturer and often include details of the device’s regulatory status (countries in which the device is marketed and date of commencement of supply), regulatory actions undertaken during the reporting period (e.g. recalls, notifications), a tabulation of incidents (particularly serious adverse events/ incidents, including deaths, stratified into whether the manufacturer considers them to be device-related or not) and estimates of the incidence of incidents.

Post-marketing data about incidents are generally more meaningful when related to usage but caution is needed. The extent of user reporting in the medical devices vigilance system may vary considerably between countries, users, and type of incident. Considerable under-reporting by users is expected. However, the analyses of data within these reports may, for some devices, provide reasonable assurance of both clinical safety and performance.

Generally, reactive PMS is focussed on device safety rather than performance (although it may be implicit...
that if there are a lack of complaints/issues, the device is assumed to be performing as intended), whereas proactive PMS (i.e. PMCF) can actively acquire evidence of device performance in line with claims made. Therefore, a manufacturer with inadequacies in the original clinical data at CE certification, but who has substantial PMS data indicating lack of complaints and vigilance, cannot simply conclude that both clinical safety and performance have been adequately addressed. The conclusion would be rather, that clinical safety may be adequately addressed, but there could remain an open question on whether clinical performance has been sufficiently demonstrated.

The outcome of the gap analysis of the available clinical data against the requirements of MEDDEV 2.7.1 rev. 4 will determine whether existing data is sufficient to support continued compliance, or most critically, whether further actions are required to address gaps. These actions are likely to fall into two areas:

1. Reinforcement of PMS data with more robust processes ensuring data gathering is as effective as possible; and/or
2. Performance of PMCF activities to fill significant gaps in clinical knowledge.

Note: In a limited number of cases, there may be the need or opportunity to revisit and reinforce preclinical design verification and validation activities to address claims that do not necessarily require direct clinical data (e.g. claims related to improved haemocompatibility compared to other devices, which might be best addressed preclinically, although - perhaps - subsequently reinforced with PMCF data demonstrating expected performance).

Early implementation of these activities will allow manufacturers to subsequently approach NBs with either a convincing package of clinical data which meets expectations, or an ongoing PMCF activity to provide such evidence. These options should potentially prevent the more draconian actions the NB may need to take in the absence of sufficient clinical data to demonstrate compliance with the new MDR GS PRs, such as reduction in scope of certification or removal of certification. It is harder for a NB to remove CE certification from a device if there are clear, corrective action steps being undertaken by the manufacturer - as long as there is no suggestion that patient safety is compromised.

Figure 6 illustrates some clinical data scenarios and possible outcomes. Scenarios 4, 5 and 6 might possibly be retrievable, but also carry a significant risk of immediate removal of CE certification by the notified body.
# Preparing for MDR Implementation with Regards to PMS and PMCF

## Scenario 1: New Product at Initial Certification 2018

<table>
<thead>
<tr>
<th>CLINICAL DATA</th>
<th>PMS</th>
<th>PMCF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOOD</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Commentary:**
Assuming that the planned PMS and PMCF are performed appropriately and provide acceptable results the clinical data is strong at the end of the MDR transition period.

## Scenario 2: Mature Product with History of Clinical Use in the EU

<table>
<thead>
<tr>
<th>CLINICAL DATA</th>
<th>PMS</th>
<th>PMCF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOOD</strong></td>
<td><strong>GOOD</strong></td>
<td><strong>GOOD</strong></td>
</tr>
</tbody>
</table>

**Commentary:**
This product can be considered the “gold standard”, with a strong clinical data package with ongoing PMS and PMCF activities supporting compliance.

## Scenario 3: Mature Product A

<table>
<thead>
<tr>
<th>CLINICAL DATA</th>
<th>PMS</th>
<th>PMCF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POOR</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Commentary:**
In this case the clinical data at initial certification is poor (perhaps with weak equivalence justification), however there is good PMS data. This may allow ongoing CE certification whilst PMCF is performed to ensure all claims are fully supported.

## Scenario 4: Mature Product B

<table>
<thead>
<tr>
<th>CLINICAL DATA</th>
<th>PMS</th>
<th>PMCF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POOR</strong></td>
<td><strong>LARGE VOLUME BUT POOR</strong></td>
<td><strong>NOT PERFORMED</strong></td>
</tr>
</tbody>
</table>

**Commentary:**
With weak clinical data at initial certification, large volume but poor PMS data lacking detail, the PMS process needs revision and PMCF is required – the NB may maintain CE certification with restricted Indications/populations if no safety concerns apparent.

## Scenario 5: Mature Product C

<table>
<thead>
<tr>
<th>CLINICAL DATA</th>
<th>PMS</th>
<th>PMCF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POOR</strong></td>
<td><strong>LIMITED</strong></td>
<td><strong>INADEQUATE</strong></td>
</tr>
</tbody>
</table>

**Commentary:**
With weak clinical data at initial certification, poor PMS data, the PMS process needs reinforcing and PMCF is required – the NB may maintain CE certification with restricted Indications/populations for PMCF if no safety concerns apparent.

## Scenario 6: Mature Product D

<table>
<thead>
<tr>
<th>CLINICAL DATA</th>
<th>PMS</th>
<th>PMCF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POOR</strong></td>
<td><strong>POOR</strong></td>
<td><strong>NOT PERFORMED</strong></td>
</tr>
</tbody>
</table>

**Commentary:**
With weak clinical data at initial certification, weak PMS and no PMCF – the NB will remove certification pending new clinical data. The manufacturer might mitigate this risk with intensive PMS and PMCF activities.

---

**Figure 6:** MDR Clinical Data Scenarios and Potential Outcomes
Reinforcing PMS Procedures and Data

The appropriate reinforcement of PMS procedures and data entails:

• Better control of distributors to ensure all PMS data is received from the distributor directly.
  o Under the MDR, distributors are economic operators with responsibility for monitoring the devices they put onto the market.
  o The legal manufacturer must ensure appropriate PMS and vigilance actions are undertaken by the distributor under full control and surveillance from the legal manufacturer.
• Ensuring complaints are logged from all sources more effectively and are investigated in a timely and thorough manner.
• More detailed analysis of complaints by region/type etc., with a thorough assessment of their impact on the overall clinical safety and performance as per GSPRs.
• Trending of PMS data to better understand and identify emerging device concerns.
• Ensuring the PMS data feeds into risk management and is incorporated into the updated CER.

Click here to access NAMSA’s PMS example template of best practice presentation of PMS information.

PMCF Study Considerations

A PMCF study may take a number of forms, including:

• Questionnaire to clinicians assessing usability of a device
• Registry of implanted devices
• Retrospective assessment of clinical outcomes
• Clinical study monitoring a specific claim which is not well supported

PMS Data Considerations

A well-developed and managed PMS process should demonstrate the following:

• A robust system, thorough with all sources of data followed up and utilised
• Detailed analysis of data (e.g. template presentation and analysis)
  o Generic statements such as “in the last five years, we have sold X units and only had Y complaints” is insufficient to provide a meaningful interpretation of post-production information
• Evidence that the PMS system is working effectively, such as:
  o Complaints proportionate to expectations, demonstrating data is being collected and analysed effectively (i.e. a manufacturer has sold 1 million units without any complaints – in 1 million units, has there really been not even one reported instance of a minor issue such as crushed packaging, etc.?)
  o Information from PMS is feeding back into the risk analysis, CER and Instructions for Use
PMCF Data Considerations

PMCF activities should:

- Meet MEDDEV 2.12-2 rev. 2 expectations.
- Provide appropriate evidence of planning, protocol execution and reporting with reasonable timelines.
- Target residual risks and confirmation of safety and performance over a device’s lifetime, and should not be trying to answer questions that should have been addressed prior to CE marking. While this is the ideal, in the case of remedial PMCF as discussed, significant questions that should have been addressed pre-CE marking, but remain outstanding, may fall within PMCF if the clinical safety of the device is assured.
- Include all targeted structured post-market activities that address specific questions/residual risks. As an example, where initial certification was based on equivalence with an existing product in clinical use in the EU. In this case, the main residual risk is that equivalence is not achieved in a real-world clinical environment, therefore the PMCF should evaluate if the device performs as intended and if it achieves expected outcomes.

What PMCF is Not....

- An expedient route to gain early CE certification and then gather critical clinical evidence later.
- A post-market study with primary objectives to demonstrate safety and performance requirements (ERs or GSPRS) which should have been addressed pre-CE marking.
- A token gesture to regulators to follow-up a few patients with a satisfaction survey that does not provide any meaningful information.

The Benefits of MDR Preparation

Although it is easy to interpret the MDR requirements as an unnecessary time and cost burden to manufacturers of devices already in use within the EU, there can be a silver lining to additional MDR activities. Enhanced PMS and PMCF activities provide the manufacturer opportunities to generate market support and health economics data which may enhance market differentiation; furthermore, the increased market knowledge gained may inform future device development programs and market opportunities.
It is also true that the time/cost implications of the preparation may result in rationalisation of device portfolios, with some manufacturers preferring to discontinue lines that may require substantial remedial action - but that in itself demonstrates perhaps that these types of devices didn’t really have a place in future clinical use.

Managing Notified Body Relationships
As mentioned previously, all stakeholders are embarking on a voyage of discovery with the new EU MDR, and NBs are no exception. They are awaiting guidance from the EU Commission and designating authorities on implementation, as well as publication and approval of implementing and delegating acts. The leading NBs (members of the industry body TEAM-NB) will have made their designation submissions to their respective competent authorities on 26 November 2017, after the six month moratorium on designation submission.

Below are helpful documents which provide information regarding TEAM-NB members intending to submit applications for designation against the MDR and/or In Vitro Diagnostic Regulation (IVDR), and the subsequent survey of NB applications against the new regulations.

- Application: Team NB MDR/IVDR
- Press Release: Survey on NBs Application against New Regulations

NBs must demonstrate their competency and procedures to meet the requirements detailed in chapter IV and Annex VII of the MDR. However, that by no means demonstrates that these NBs know all the criteria for MDR implementation (as many remain yet to be determined, as demonstrated by the CAMD MDR/IVDR Implementation Roadmap, found here).

A learning curve is to be expected for all stakeholders, as it was when EU MDD was first launched in 1993. Therefore, the best option for manufacturers is to demonstrate that they have been proactive in MDR preparation, candid in their clinical gap analysis, and robust in the reinforcement of PMS and PMCF initiatives when necessary. NBs will want to avoid withdrawing certification if at all possible, but the strength of a manufacturer’s case to support ongoing conformity to requirements will ultimately decide the outcome.

Early engagement with a manufacturer’s NB should help smooth the process, and is highly recommended. Some key points to address with an NB include:

- Has the NB applied for designation under the MDR?
- What is the scope of application for designation (i.e. what products will they be able to certify)?
- When is the Joint Audit Team (JAT) audit scheduled?
- What is the expected date of designation?
- What information is available to address:
  - The transition plan for clients moving from MDD to MDR?
  - When the NB will no longer issue MDD certificates?
  - What is the approach for existing CE marked devices?
- What is the approach for new submissions, when is the latest that MDD submissions for new products will be accepted?
- What are the critical cut-off dates?
- How will the validity of existing MDD certifications be addressed after 26 May 2020?
- If the NB is in the UK, how is the Brexit issue being managed:
  - What contingency plans are in place?
  - What are the critical cut off dates?

**A Note Regarding the Use of MEDDEV Guidance Documents**

All MEDDEVs contain the preamble that "the guidelines are not legally binding," that is to say that only the Directives (93/42/EEC, 90/385/EEC) are the legal documents. However, the EU Commission states:

*The MEDDEVs promote a common approach to be followed by manufacturers and Notified Bodies that are involved in conformity assessment procedures.*

- The MEDDEVs are drafted by authorities charged with safeguarding public health in conjunction with all stakeholders; industry associations, health professionals associations, Notified Bodies and European Standardisation Organisations. This is in accordance with the relevant annexes of the directives.
- MEDDEVs are carefully drafted through a consultation process with all interested parties and are subject to a regular updating process.
- These documents have particular reference codes and are endorsed at the Medical Devices Expert Group (MDEG) plenary meetings.
- The guidelines are not legally binding. **However, due to the participation of the aforementioned interested parties and the experts from competent authorities, it is expected that the guidelines be followed, ensuring the uniform application of relevant directive provisions.**

As a result, manufacturers are advised to adhere to the expectations of the MEDDEVs, unless there is a compelling argument to demonstrate the MEDDEV is not applicable to a manufacturer’s device.

Although there is uncertainty whether MEDDEVs in their current format will remain upon date of application of the MDR, the CAMD Executive Group implementation roadmap includes updating/addenda of existing MEDDEVs, so it is likely these types of documents will remain (as there is substantial need for guidance), although perhaps under a different guise.

**Conclusion**

The date of application of the MDR is fast approaching (26 May 2020), and NBs are only expected to be designated in early/mid-2019. As a result, there will be limited time to get devices CE certified against MDR requirements. While reinforcing clinical data via PMS and PMCF is a time-consuming process, the current window of opportunity allows manufacturers time to address shortfalls and ensure they are in a good position to maintain CE certification when the MDR transition period ends...but only if manufacturers take action now.
References


About NAMSA

NAMSA is a Medical Research Organization (MRO*), accelerating medical device product development through integrated laboratory, clinical and consulting services. Driven by our regulatory expertise, NAMSA’s MRO* Approach plays an important role in translational research, applying a unique combination of disciplines—consulting, regulatory, preclinical, toxicology, microbiology, chemistry, clinical, and quality—to move clients’ products through the development process, and continue to provide support through commercialization to post-market requirements anywhere in the world.

NAMSA operates 13 offices throughout North America, Europe, the Middle East and Asia, and employs 1,000 highly-experienced laboratory, clinical research and regulatory consulting Associates.
