WHITEPAPER

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Three Key Stages – Three Common Pitfalls

Post-Market Clinical Follow-up Under MDR

AN INSIGHT PAPER BROUGHT TO YOU BY THE UNRIVALED COLLECTIVE EXPERTISE AT RQM+

MAY 2021

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Summary

- The European Commission extended the implementation deadline for compliance with the EU Medical Device Regulation (MDR) by a year – the new deadline is now quickly approaching in May 2021
- This extension was designed to give medical device and in vitro diagnostic manufacturers a chance to achieve full compliance while also handling business disruption resulting from the COVID-19 crisis
- However, this deadline delay may also be lulling some manufacturers into a false sense of security, slowing down efforts to comply which may already be behind schedule
- There is also a well-recognised capacity issue among the Notified Bodies that are authorised to validate compliance, so any slowdown in preparatory efforts may have serious adverse commercial implications, especially given that the EU in vitro diagnostic Medical Device Regulation (IVDR) is coming on the heels of MDR
- Specifically looking at Post-Market Clinical Follow-up (PMCF), where the bar for supporting data quantity and quality has been significantly raised by MDR, it is imperative to maintain the momentum of preparatory efforts
- Our work with clients has revealed a number of common pitfalls that have emerged, each of which could have significant commercial consequences if not addressed
- This short paper aims to highlight those common pitfalls, alongside a reminder of the three main best practice steps to compliance, to help manufacturers optimise their competitive positioning

MDR preparation and the COVID-19 crisis

As vaccine programs swing into action and the world begins to recover from the 2020 experience, this short paper is designed to provide a fresh, positive perspective on Post-Market Clinical Follow-up (PMCF) planning. The requirement for PMCF planning has not reduced, even though budgets may have changed because of pandemic pressures. Ultimately, good planning will deliver optimal results in PMCF compliance. In a changed world, the good news is that there need be no sacrifice of quality if adequate preparation is prioritized.

This paper reviews the pandemic pressures that have arisen, and aims to provide guidance to overcome potential pitfalls. It offers a clear planning strategy that will build a strong rationale and justification for PMCF activities that is easily defended and/or discussed with your notified body.

Even before the COVID-19 crisis hit home in early 2020, there were concerns about the implementation timeline of the EU Medical Device Regulation (MDR). The MDR involves a huge step change in the EU regulatory framework, and the ability of medical device companies to prepare effectively for its original May 2020 implementation deadline was being hampered by various capacity uncertainties (1). This was making many players question whether or not it was worth introducing or maintaining certain products in the EU market (2).

The European Commission then extended the MDR deadline by an additional year to May 2021. This gave medical device manufacturers additional breathing space to achieve compliance, and a chance for the less prepared organisations to catch up. Different pressures and urgencies have arisen: the in vitro Diagnostic Medical Device Regulation (IVDR), has not been postponed (3,4), putting MDR and IVDR deadlines even closer to one another. Therefore, despite the delay, it is still important to keep an eye on the ball in terms of MDR preparation and readiness. And the resources required to make those preparations are considerable (5,6).

MDR preparation and the COVID-19 crisis

In addition, concerns over the Notified Bodies' capacity to meet the demand has not diminished – in fact, quite the opposite (7). In the pandemic situation, research for the European Commission noted that "16% of notified bodies are not taking any new applications...reduced to 8% when considering applications related to a change notification (8)."

Despite these pressures, a systematic and smart approach to the various aspects of compliance is perfectly achievable, so long as certain factors are carefully considered in the preparatory phase.

At RQM+, we are supporting our clients with clinical regulatory strategies that balance regulatory, clinical, and business needs and risks. We focus on telling the complete story of sufficient clinical evidence which includes both the CER and PMCF plan. The end results are fewer NB questions, shorter review times, and not just MDR compliance but overall business success.

Lisa Casavant, EVP, RQM+

The positive outlook that this short paper summarises, helps to point out some key potential pitfalls specifically relating to PMCF, how to avoid them, and how to keep your preparation programme on track, efficient and effective.

Post-Market Clinical Follow-up under the spotlight

Providing clinical data to support the safety and performance of devices is one of the key aspects of the MDR. The new regulation sets stricter requirements for clinical evaluation and places a much stronger focus on pre-market clinical investigations as well as collecting clinical data through pro-active Post-Market Surveillance (PMS) activities, including Post-Market Clinical Follow-up (PMCF). It is important, therefore, for manufacturers to determine what clinical data is needed for their devices prior to MDR review of their products.

Clinical trials are unquestionably being heavily impacted by COVID-19. In an atmosphere of "all hands-on deck (9)" among health care providers around the world, research unrelated to COVID-19 treatment and vaccination is being de-emphasized (9). Inevitably, this means PMCF data collection through clinical studies prior to the MDR, which may be needed to gain CE marking under the MDR, may suffer on account of reduced opportunities for patient eligibility and collection of postoperative data.

In the light of these new pressures caused by the pandemic, this short paper revisits best practice in achieving compliance with the PMCF requirements in the MDR, and presents lessons learned to date on the most likely pitfalls that manufacturers are encountering on this journey.

PMCF Plan – EU Medical Devices Coordination Group 2020-7 Guidance

- A PMCF plan shall specify the methods and procedures to proactively collect and evaluate clinical data from the use in or on humans of a CE marked medical device.
- Aim of the PMCF Plan is to:
  - Confirm safety & performance throughout device's expected lifetime
  - Identify previously unknown/monitoring known side effects
  - Identify and analyze emergent risks
  - Ensure continued acceptability of benefit-risk ratio
  - Identify possible system misuse or off-label use of device
- A continuous process that updates clinical evaluation and shall be addressed in the manufacturer's post-market surveillance plan
- Part of the Clinical Development plan and PMS Plan

See: MDR Annex XIV Sections 5 & 6; IVDR Annex XIII Part B

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PMCF: three key stages – three likely pitfalls

Based on the RQM+ team's advisory experience from the last two years, this short paper now reviews three major PMCF pitfalls which manufacturers are often falling into.

Ultimately, if not avoided, these pitfalls may have very serious business consequences, including products being pulled from the market and/or certifications suspended. The financial implications do not bear thinking about.

This paper is designed to offer practitioners a best practice guide covering preparation steps and the three key pitfalls which RQM+ is most frequently encountering.

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PMCF Best Practice Step 1 : Standardize assessment and identification of data

Adopt standardized assessment for all products – this is the first step in enabling meaningful communications and comparisons across the corporation. A standardized approach to data assessment ensures consistency across devices; ensures areas are not missed when workload is divided; aids prioritization at later stages; and presents information consistently for effective comparison. For this assessment, the approach should enable the clinical data to be organized so that it is clear what data is available for each device, medical indication, and target population. It may be necessary to update the clinical evaluation prior to identifying all relevant data so make sure you leave enough time to do this.

Contextualise data in wider risk framework – This might include complaint trends, complaint severity measures, adverse events, recalls/FSCAs (10)/FSNs (11), sales data, changes in specific marketing regions, political risk, hazard legalities, etc.

PMCF Probable Pitfall #1: Defining 'Sufficient Clinical Evidence'

Perhaps the principal pitfall that companies are encountering in the PMCF compliance journey is deciding precisely what 'sufficient clinical evidence' means. It has to be clearly understood that interpretation of the word 'sufficient' involves an interplay between quantity and quality. Do we require feedback from 3 patients... or 30 patients... or 300 patients? And is that feedback providing meaningful answers that directly correlate to product performance? The answers to these questions will largely depend on the risk class of the device, the indication, claims, available data to support the device, and any recent changes in clinical practice. Ruthless rigour is required when assessing clinical papers as supporting data. We have seen instances where companies have been tempted to list literature which is certainly about the product, but is not looking at relevant outcomes. Analysing outcome data from high quality studies that are relevant to the intended use of the device and comparing the results to similar devices or other treatments is an important component to determine whether sufficient clinical data exists for the device.

PMCF Best Practice Step 2: Review available data

- Identify gaps – Once the clinical data for each device has been collected and organized, existing clinical data gaps or emerging risks should be determined from Notified Body reviews, Clinical Evaluation Reports, and Post-Market Surveillance and Risk Management reviews.
- Interrogate data quality and appropriateness – how meaningful is the data collected or literature cited? Does the data support the safety and performance of the device and intended use of the device? Is this the level of evidence the notified body is going to expect for this risk class?
- How can gaps be filled most effectively/efficiently? Can they be supported with SOTA (12), risk level, compliant data, or market experience? Does it need to be made more specific for each indication? Does it include appropriate outcomes to support the clinical benefits? Is there bias that needs correcting? How much of it comes from Post-Market Surveillance? Does the follow-up represent the entire product lifetime? And are all product variants and ranges covered in the clinical data?
- Assign ownership, with clear matrix of responsibilities within product teams (tech doc, Instructions for Use, product claims, SOTA (13)), then across Clinical and Performance, Regulatory Affairs, Product Quality and Sales & Marketing
- Understand level of device-specific needs across product portfolio. This requires alignment with the broader PMS, Marketing, R&D and General Management teams. For a start, the resources per device will be prioritized by certificate expiration timeline, gap analysis, likely lifecycle (Implants), sheer volume of devices requiring data remediation, and role of product within larger therapeutic systems.
- Yet... the system must flex to individual requirements per product, each of which will be unique. How would the data be presented to an auditor? How does your data vary by device, in terms of classification, breadth of indications, novelty or market history? What are the available options appropriate to class of device and clinical gaps? Are there WET (14) exemptions, or is a lower data bar acceptable/advisable?
- PMCF preparation will inevitably reveal a number of hard commercial choices that need to be made within a limited period of time – namely, whether or not to keep all products in the current range on the European markets. Those who have moved early in their preparations are finding themselves better able to take that view, and less pressurised to withdraw market presence.

PMCF: Probable Pitfall #2: Aligning with other departments

The next major pitfall that we are encountering in our work with manufacturers is a failure to align early in the process with other departments outside of clinical, such as Sales & Marketing or General Management. Attaining buy-in from other stakeholder business units is crucial for PMCF success and ongoing regulatory compliance.

The reason it is critical to emphasize cross-functional alignment is that this scrutiny and clinical evidential basis applies equally to legacy devices as to new products. In fact, these pitfalls are probably most acute with legacy devices that have been established on the market for a long time. Non-specialists in the business are asking, "Why do we need to spend on compliance now for highly established products?" The fact of the matter is that such clinical evidence is required under the new Regulation. And there are often significant costs associated with obtaining sufficient data – volume and quality/relevance. Therefore, it is important to align on device priority, submission risk, and all available sources of data on a product for these activities.

We hope it is now clear why it is an important process to bring other departments along, and help them understand why they need to care, why they need to fund, and the potential business damage from poor data quality and non-compliance.

PMCF Best Practice Step 3 - Develop compliant PMCF strategy

- Understand options for your PCMF strategy – cost & effectiveness per device class & gaps. Effort and cost are least for clinical literature reviews, rising through patient and customer surveys/questionnaires, to clinical database information, right up to clinical RCTs. This all goes to build the strongest possible, minutely documented, rationale for PMCF data inclusion/exclusion, depth and relevance.
- Understand ideal combination of people, systems and skills needed for the most economical solution. What activities need to be in house and which are better outsourced? In times of extreme market pressure (COVID, MDR, IVDR, etc), then skills and resources are in short supply, even when properly budgeted.
- How does your PMCF strategy interface with Notified Bodies? NBs are strictly forbidden from offering "consultancy or advice to the manufacturer, the authorised representative, a supplier or their commercial competitor as regards the design, construction, marketing, or maintenance of the products under assessment.(16)"

However, there are ethical opportunities to interact with the NB. Regular meetings with the scheme manager can be used to present plans and rationales for confirmation. **Change notices are a good time to include PMCF plans, and early EU MDR submissions should be considered where possible.**

Business Considerations for PMCF Activities

*refer to MDCG 2020-6 Appendix III

PMCF Activity	Cost of Activity	Time to Complete Activity	General vs. Specific Data	Device Class	Documentation/ Available Clinical Evidence
Data retrieved from the literature	$			I, IIa, IIb, III	
User Feedback Surveys	$$				
Patient-Level Data Surveys (Individual Case Reports)	$$$				
Device Registry	$$$$				
Retrospective Cohort Study	$$$$				
Post-Market Clinical Investigation/ Independent Clinical Studies	$$$$$				

- Have rigorous justification for PMCF strategies, that will stand the test of close scrutiny. Justifications should follow sound scientific principles, with clear, measurable objectives and deep documentation. Economic reasoning (high costs) to justify risk-taking is never a sound option. Business considerations for each PMCF activity should be thoroughly assessed. Factors we recommend including in the assessment include: timeline of the activity, available budget, risk class of the device, quality of data needed to support sufficient evidence, and whether a general or specific PMCF activity will provide the data required.

PMCF: Probable Pitfall #3: Not enough detail in documentation

MDR introduces a much higher bar for clinical evidence, even when introducing small changes to established products, such as an anti-microbial coating, or a slight difference in manufacturing method or material.

Our third most frequently encountered PMCF compliance pitfall is a reluctance to put enough detail into the documentation. Even though the Medical Device Co-ordination Group (15) and the Notified Bodies seek to make it abundantly clear about the level of detail expected, too many companies are not taking this to the required depth.

It is critical to make sure that the amount of PMCF required and the associated justification fits the proposed strategy using sound scientific principles, clear and measurable objectives, and robust statistical planning. Document the proposed data and justification, document the underlying rationale vs risks, and then document the references (footnotes to EU MDR, guidance, etc). In addition, the statistical rationales sitting behind the level of detail and data quality provided are often insufficiently robust.

These are the justifications for why the proposed level and type of clinical data is appropriate based on the risks associated with the device. Also, consider pre-defined trigger points for action in advance. Finally, if you are choosing not to do something, that choice must also have the most robust possible rationale.

Next Steps

Draft and test process with a few representative and high-priority devices to start with – to pilot and refine the process from drafting the PMCF plan to completion of the PMCF report. This will road-test templates, forms, and processes to demonstrate that they work well across your company. It is also important to **remember that the PMCF process is not an isolated 'once and done' process**. The manufacturer needs to consider how the PMCF process is integrated with the PMS process, clinical evaluation, and risk management process, and determine how the documents are going to be updated over time.

This short paper has attempted to highlight some of the emerging challenges that medical device and IVD manufacturers could encounter, in respect of MDR compliance preparation (and PMCF in particular). By ensuring your organization has a robust PMCF strategy in place, manufacturers can avoid significant financial and market access implications down the line. **Getting prepared for MDR and IVDR in good time (even early, if possible) requires a balance between in-house skills and outsourced expertise**. Partnering with third party experts who have both knowledge and experience in this area, can help medical device companies to develop and implement successful PMCF roadmaps.

If you would like to discuss your company's situation to avoid the common pitfalls outlined in this paper, please contact the RQM+ team at info@RQMplus.com, or visit RQMplus.com.

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Webinar: Best Practices in Scientific Database Searching

RQM+ Live! #6 PMCF Process in Action: Best Practices for MDR Compliance

PMCF Plans: How to create detailed, compliant, and business-balanced PMCF plans

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