MDR COMPLIANCE: PLANNING FOR POST-MARKET CLINICAL FOLLOW-UP

In this article, Celeste Maksim, PhD, Chief of Staff, Clinical and Post-Market Practice at RQM+, discusses best practices for drug delivery device manufacturers when conducting post-market clinical follow-up activities, as mandated by the EU Medical Device Regulation.

While the EU Medical Device Regulation (MDR) came into force in May 2021, many manufacturers benefitted from the option to renew their certificates under the previous Medical Device Directive (MDD), granting them an extended period to transition to MDR compliance, ending in 2024. However, some requirements already applied to all manufacturers, regardless of whether or not they are taking advantage of the extension; Article 120 of the MDR states that post-market requirements will apply to MDD-certified devices even during the transition period. Post-market activities are extensive under the MDR and require ongoing attention. This article will focus on post-market clinical follow-up (PMCF), which falls within the MDR's post-market surveillance (PMS) plan.

The aim of PMCF is firstly to confirm the safety and performance of a device, including the clinical benefit, if applicable, across the span of its expected lifetime. It also helps to address risk by identifying previously unknown side-effects, monitoring the identified side-effects and contraindications, and identifying and analysing emergent risks on the basis of factual evidence. The conclusions of this analysis are then used to demonstrate the continued acceptability of the product's benefit-risk ratio. Furthermore, PMCF activities can identify possible systematic misuse or off-label use of the device.[1]

Pharmaceutical companies must be aware of PMCF requirements, particularly if they:

- Manufacture medical devices
- Partner with or supply to companies that manufacture medical devices
- Manufacture a drug that is sold pre-packaged in a delivery device.

STRATEGY

As PMCF is a long-term activity that must be carried out throughout the lifecycle of a device, it is paramount to establish sound strategies and clear processes for it as soon as possible. Ideally, strategies should take a holistic approach, incorporating all relevant departments within an organisation. PMCF is likely to require significant resources, even for legacy devices that have been on the market for a long time, and input will be required from multiple departments and functional areas within the company. Therefore, it is important to involve each department in discussions and decision-making, making them aware of the rationale for PMCF activities and the potential business damage of non-compliance.

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The available activities for PMCF include randomised clinical trials, registry studies, retrospective patient chart reviews, literature reviews, end-user surveys and focus groups; appropriate activities need to be carefully selected from this list. A recommended approach is to stratify the clinical evidence to determine the appropriate PMCF activity and identify the objectives, primary endpoint and acceptance criteria for each product. Transparency with all stakeholders should minimise the potential side-effects of compartmentalising activities within the company.

It is also helpful for all departments to understand how data links together throughout the post-market lifecycle. Gantt charts by document and data input/source have proven helpful for optimising strategies, and for understanding the resource requirements for ongoing MDR compliance. For example, discuss with safety and

Dr Celeste Maksim
Chief of Staff, Clinical and Post-Market Practice

RQM+
2790 Mosside Blvd
Suite 800
Monroeville
PA 15146
United States

www.rqmplus.com

complaint handling teams how complaints will be handled prior to conducting a complaints-related PMCF activity.

PROCESSES

New clinical data obtained through PMCF should be fed into ongoing clinical evaluation, and post-market documents need to be regularly updated. Inconsistent procedures and data organisation will inevitably make PMCF compliance a much greater challenge than it needs to be. Data should be presented in a standardised manner across all devices, medical indications and target populations, making it easier to evaluate existing clinical data, contextualise and track changes, and prioritise.

Crucially, standardised processes should support a notified body review, as they produce a consistent clinical story across all documents in the submission, and in documents supporting ongoing compliance. Processes may need some adjusting once they have been tried out, so it is good practice to test processes with some representative high-priority devices first. This helps to gauge whether the proposed templates, forms and processes will work well across the company.

PRIORITISATION

It may not be realistic for a company to achieve PMCF compliance for their entire product portfolio overnight. As a result, they may need to assess the quality and relevance of existing clinical evidence and determine which devices are closest to meeting PMCF compliance requirements and which need more work. They can then decide which devices to prioritise while also considering revenue, certificate expiration timelines, likely lifecycle, market strength and the number of devices in need of data remediation. If there is not enough time to carry out the most appropriate PMCF activity for a device, manufacturers can demonstrate how this will be remedied over a multi-year period and which activities will be employed. In some cases, it may be possible to obtain PMCF clinical data during notified body review, which can then be used to answer post-submission queries from the notified body.

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DATA & DOCUMENTATION

PMCF must be based on what the regulation refers to as "sufficient clinical evidence". What exactly the regulation means by "sufficient" can be a source of confusion for manufacturers. The amount of data required varies depending on the risk class of the device, the indication, claims, available data to support the device and any recent changes in clinical practice or the device itself. Manufacturers should ensure that their data clearly support the intended use of the device, demonstrate clinical benefit and support the indications and claims. They can also compare the outcomes achieved with similar devices on the market that are considered state of the art treatment options, to determine whether they have sufficient clinical data.

It is critical to be able to provide a strong rationale for why the available data should be considered "sufficient". A common remark from notified bodies is that manufacturers are not providing enough detail on decisions in their documentation. All decisions, however obvious, should be explicitly rationalised and supported with all relevant data, documentation, regulatory references and statistical rationales.

COMPLIANCE URGENCY

The expectations placed on the quality and quantity of data are higher under the MDR. To meet these expectations, best practice is to plan thoroughly from the outset. With notified bodies under severe pressure, it is advisable for manufacturers to complete outstanding compliance tasks as soon as possible. A high volume of MDD certificates are expected to expire in 2024, which may then lead to delays in notified body reviews. Timely compliance will allow manufacturers to benefit from the attention of a notified body before the rush of submissions expected in two years' time. Although notified bodies cannot offer consultancy or advice, manufacturers can liaise with them post-submission to understand their queries and the meaning of any non-conformities raised.

The advice provided in this article is intended to help manufacturers plan for high-quality submissions that require minimal remediation and to implement best practices in their PMCF activities.

ABOUT THE COMPANY

RQM+ is a leading international provider of regulatory, quality and clinical consulting services for medical device and diagnostics manufacturers. RQM+ delivers transformative solutions to clients by providing collective knowledge and expertise, fuelled by passion for client success. RQM+ experts are collaborative, laser-focused on client needs and committed to delivering high-value solutions that exceed expectations.

REFERENCE

1. *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.*

ABOUT THE AUTHOR

Celeste Maksim, PhD, is Chief of Staff, Clinical and Post-Market Practice a RQM+. She is RAC-certificated, has a PhD in analytical chemistry and has over a decade of experience in regulated industries, including pharmaceuticals, medical devices, and *in vitro* diagnostic products. Dr Maksim's main focus at RQM+ is on building and managing PMS & PMCF/PMPF services.