Are you ready for the new EU Medical Device Regulation?

Summary of session 5

The transition period for the new medical device regulation (MDR) on the European market ends in May 2021 and by becoming effective, MDR will have a great impact on all medical device actors, throughout the lifecycle of devices, with stricter requirements on both products and on the Quality Management Systems. Post-market surveillance (PMS) is an important part of the regulatory framework for medical devices in Europe and is required regardless of the classification of the medical device, however the details of the requirements differ. In this fifth and final session, Tina Amini summons up the need to knows regarding post market surveillance and MDR.

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The need for a post market surveillance system (PMS) system is given in Article 83 of MDR. MDR requires manufacturers to plan, establish, document, implement, maintain, and update a PMS system that is proportionate to the risk classification of the device and appropriate for the device type. PMS refers to 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 have placed on the market throughout the entire device lifetime. It should be an integral part of the quality management system.

PMS is needed because a residual risk with regards to safety and performance may remain throughout the entire lifecycle of the medical device. This could be due to a combination of factors, such as the medical device's use environment, the different end user interaction, as well as unforeseen medical device failure or misuse. Design and development activities of medical devices ensure that the residual risk is acceptable before the product is put on the market. However, it is important to have an appropriate system to continuously collect and analyse information on the devices both during production and postproduction, to allow early detection of any undesirable effects and to ensure the residual risk remains acceptable. These processes can reveal opportunities for improvement of the device such as usability, performance and safety of the device. If a need for corrective or preventive actions is identified during the PMS the appropriate measures must be implemented and if necessary, the competent authorities and notified body concerned must be informed.

According to MDR article 84, the PMS system should be based on a PMS plan which will be

part of the technical documentations reviewed by notified bodies (NB). PMS plan contents are given in MDR Annex III.

General framework for PMS Plan:

- Scope
- Objective
- Responsibility (functions, not individuals)
- Timelines
- Data Sources
- How to Analyse the Data
- Reporting on Data Analysis
- Review of Plan

The extent of the scope depends on the risk classification and type or complexity of the device. It is recommended to include the medical device type or family, its lifecycle stage in relation to state of the art, the classification, countries where its sold, the expected lifetime of the device or the expected frequency of use, and basic information on the intended use and safety and performance data. ISO/TR 20416:2020 is a useful document for drafting the PMS plan as it helps to establish a common understanding of the PMS process.

To formulate the objectives of the plan, you can use questions such as:

- Any new hazard or hazardous situation identified?
- Any unforeseen side effects?
- Any misuse of device?
- Does device meet user's needs after medium/long term clinical use?
- Has state of the art changed since?
- Any usability issues?
- Is the expected lifetime correct?

When defining the objectives of the PMS plan, manufacturers should specify the measurable associated criteria, alert, and action levels as well.

Regarding data sources, one can refer to article 84 and Annex III of MDR which require the PMS plan to address the collection and utilisation of following information:

- information about serious incidents, field safety and corrective actions
- records, referring to non-serious incidents and undesirable side effects,
- information from trend reporting,
- relevant specialist or technical literature databases or registries
- information including feedbacks and complaints provided by users, distributors, and importers, practically anybody in the supply chain
- publicly available information about similar medical devices

It is the responsibility of the manufacturer to determine and document the sources of information used for PMS along with the frequency of collecting such data.

The source of the data and the data collection should be a combination of proactive and reactive (passive) activities. Proactive data anticipate and characterise events before they occur, i.e., user surveys, user interviews, manufacturer sponsored registry studies, clinical data from hospital data management service centres, or PMC studies. While reactive or passive are those activities which are taken after an event has happened i.e., complaints, serious injury or death, review of service/maintenance reports or regulatory compliance notifications. Relying solely on complaints to make a conclu-

sion on the benefit/risk analysis of the device is not an acceptable approach.

The PMS plan should define methods, tools, and protocols to allow correct characterisation of the device performance and to allow comparison with similar devices available on the market. The plan should define how the complaints will be investigated and how the events subject to trend reporting will be managed. Communication methods with regulators, NBs, users and other economic operators should also be defined along with effective tools to trace and identify devices in needs of corrective actions to say the least.

PMS plan should also include the proper way(s) to analyse the collected data which depends on the type of raw data collected. Manufacturers need to associate an analysis method with each source of data and define suitable indicators and threshold values for continuous benefit-risk analysis to demonstrate compliance to Annex III. The method of data collection and analysis must be justified and documented in detail with an assigned responsibility and timeframe.

Post Market Clinical Follow-Up (PMCF) is part of the clinical development plan and PMS plan. PMCF is a proactive process that collects and evaluates clinical data from use of device ensuring continued benefit-risk ratio acceptability. PMCF study is a study carried out following marketing approval intended to answer specific questions relating to clinical safety or performance (i.e., residual risks) of a medical device when used in accordance with its approved labelling. These studies may examine issues such as long-term performance, clinical events which were not apparent initially, events specific to defined patient populations, the performance of the medical device in a more representative population of providers and patients or help to identify possible systematic misuse/off-label use of device.

PMCF must be performed according to a documented plan, template of which is provided in guidance document published by MDCG (MDCG 2020-7). According to the guidance document, the PMCF plan should include document information, manufacturers details, the EU representative details (if applicable), the person responsible for regulatory compliance, device description and specification. The specific objectives addressed by the PMCF, any relevant harmonized standards, or common specifications or guidance documents used should also be detailed in the plan. PMCF Plan should also identify and evaluate the clinical data relating to equivalent or similar devices along with the relevant information from the clinical evaluation report or risk management file which are to be analysed, followed up or evaluated. Scientifically sound methods (general and/or specific) with specific endpoints, a rationale for the appropriateness of the methods used and the timelines of each activity (at least annually) should also be defined in the PMCF plan.

Examples of general methods for data collection:

Clinical literature:

- Review of literature on own device
- For well-established technologies leverage clinical data on comparator devices
- Utilise to continue demonstrating state-of-the-art

PMCF Surveys:

- Customer surveys/questionnaires
- Focus groups/expert user groups
- Feedback from users
- User reaction during training programs

Examples of specific methods for data collection:

Registry /Database:

- Review of relevant retrospective data from patients or users
- Review of data derived from a device or implant registry
- Registries (national public registries) & databases

Clinical investigations (extended follow up from pre-market study, prospective, retrospective or combinations thereof)

PMCF Survey

The PMCF survey collect clinical data which are observational in nature. When the survey is designed around well-defined clinical endpoints and acceptance criteria, it can collect real world data. The survey plan should have a clear objective which can be formulated after identifying the clinical and gaps in postproduction safety. The main challenge with the survey is to ensure the users complete and return the survey.

PMCF survey needs to identify all variants of devices within the scope, include plans for data analysis plan, statistical analysis with defined sample sizes, drawing conclusion and running the survey. The data collection methods are not required to be validated necessarily however; it is best to put in place good clinical practice requirements.

PMCF activities and the results of data analysis must be analysed and documented. PMCF report template is given in MDCG 2020-8 and should be used when manufacturers are preparing their PMCF reports.

The decision for not conducting PMCF studies must be based on a documented robust scientific rationale. Possible - but not guaranteed - justification for not conducting PMCF are if the device has common specifications, harmonized or other technical specifications, is a well-established technology, is a low-risk device/for a low-risk patient population or there has been no emerging information (new techniques, changes to state of the art, stable clinical guidelines). To justify not conducting a PMCF study, however, can be proven challenging.

Periodic Safety Update Report (PSUR)

Depending on the classification of your device, you need to prepare either a PSUR or PMS report. Article 86 of MDR states: The conclusions of the benefit-risk determination, the main findings of the PMCF, the volume of sales of the device and an estimated evaluation of the size and other characteristics of the population using the device and, where practicable, the usage frequency of the device. Class IIa, IIb, and III products are required to have a PSUR and it needs to be updated annually for Class III and Class IIb implants, and at least every two years for Class IIb (non-implants) and Class IIa devices. The PSUR must be available to your notified body, and upon request, the competent authorities.

Your PMS efforts will inform several other processes, including risk management, clinical evaluation, and activities to meet regulatory requirements. The output of PMS - including PMCF activities that continuously update the clinical evaluation - should be used to confirm the overall safety and performance of a device throughout its expected lifetime, the continued acceptability of identified risks, and to detect emerging risks based on factual evidence.

Tina's recommendations regarding Medical Device post market surveillance (PMS)

- PMS system should be based on a well-defined PMS Plan covering all device variants.
- PMS data collection is a combination of both proactive & reactive activities.
- PMS plan must be reviewed regularly to ensure its adequacy.
- Before preparing PMCF Plan ensure the clinical evaluation report is reviewed and any gaps in clinical data is identified.
- Determine which PMCF activity/-ies will be appropriate for your device type and classification
- PMCF is not equivalent to clinical investigation. There are alternative ways of collecting data.
- A robust justification should be included if PMCF is considered not unnecessary.
- PMCF plan and report templates are provided in MDCG guidelines.
- PMS output including PMCF data should be used to update clinical evaluation, risk management, labelling/IFU/claims, intended use & technical documentation at least.
- Ensure the data generated will satisfy MDR requirements & NB scrutiny in audits.

About the host

Dr. Tina Amini has over 30 years' regulatory expertise within the pharmaceutical industry as well as in Notified Bodies. At NDA, Tina supports MedTech and Pharma companies with their medical devices, in vitro diagnostic devices (IVD) including companion diagnostics and combination products. She successfully helps companies to identify the correct regulatory pathway for their borderline products and classification of their devices and has assisted clients in selection and interaction with Notified Bodies for certification of medical devices.