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Post Marketing Surveillance Compliance in Medical Device Applications

Dr. Manickam Tamilselvi[1], Dr. Ankanagari Srinivas[2]*

[1]Pharmnova Medical Research Pvt Ltd, Plot No 12, 6, George Avenue, Rajeshwari Nagar, Selaiyur, Chennai, Tamil Nadu 600073 India
[2]Asst. Professor, Dept of Genetics, Osmania University, Hyderabad, Telangana 500007, India

[*]**Address for correspondence: Dr. Ankanagari Srinivas**
email: srinivasmessage@gmail.com

ABSTRACT

At present, post-market surveillance (PMS) is getting more attention and an important requirement for all over the world markets of medical devices after EU MDR regulatory requirement is released in the year of 2017. Global Harmonization Task Force (GHTF), which defines the specific tasks needed for post-market surveillance in the industry harmonized across the world regulatory environments. A systematic procedure to proactively collect, review and implement in case of any CAPA when devices are placed on market for consumption and ISO 13485:2016 requires manufacturers to maintain a PMS system mandatory. A compliant PMS plan should consider information concerning serious incidents, records of non-serious incidents, available data on side-effects, information from trend reports, any feedback or complaints provided by users, distributors, or importers of the medical device, and publicly available information about similar devices. Regulatory requirement is emphasizing post-market surveillance and risk management for all the products available in the market. Manufacturer need to comply regulatory requirements of PMS system in order to market their products around the world.

Keywords: Medical device, Post Marketing Surveillance, EUMDR, QMS, safety

INTRODUCTION

Post marketing surveillance is the monitoring process to ensure the device safety for patient use prior to release the product in the market. There has been a multiple ways of reporting *viz* reporting to database, patient registries or any other health data base. Releasing the device prior to market, safety, quality, and the intended purpose of the device will be tested by using the smaller number of people, but the outcome of the clinical trial may not exactly imitate the medical conditions which is existing in the general populations [1]. After the device release in the market, it is used in wider populations. Thus, after marketing the device performance should be monitored and report the same to the regulatory authorities, since it is dealing with patient safety. These reported data are reviewed critically due to its high importance in relation to the patient safety.

In UK the Yellow Card Scheme (Medicines and Healthcare Products Regulatory Agency - MHRA) and the Commission on Human Medicines (CHM)) are one among the pioneer reporting system in case of any adverse drug reactions (ADRs) related to drug or device. Most of the device will have medium to high risk thus clearance from the regulatory bodies to prove its safety, quality and its performance throughout the lifecycle of the device is very essential to conclude necessary actions in order to prevent any abnormal occurrence in the patient population as per the EU MDR regulations. Any ADR should be reported to European commission by the competent authorities and notified bodies through manufacturers [2]. Manufacturers can invite notified bodies to audit their QMS as per current and revised regulations in medical device. At present the condition is that the manufacturers invest money on training their own staff to have knowledge in regulatory experience, clinical data, quality management to comply current regulatory norms in their production process in order to empower them to handle on their own (compliance).

A continuous and thorough data collection, analysis, evaluation and reporting of post-market surveillance information is one of the important criteria as per MDR regulation based on the risk of the device and to have more strict measures on patient safety. This is a legal compliance with EU MDR includes PMS plan, and PMCF plan for device specific and clinical evaluation report, which is collected continuously and evaluated for its safety and intended purpose and indication, and is one of the main criteria for technical compilation. The main objective is to confirm continued patient safety, intended clinical performance and patient benefit(s) of the device throughout product expected lifecycle.

Post marketing surveillance (PMS) studies refers when the medical device is used in real time studies with patients in clinical practice and involve systematic monitoring. Monitoring of medical device during post marketing surveillance as per the new European Union Medical Device regulation which is covered in the Article 83, 84, and 86 [2] is used in standard clinical practice, in which study conditions are rigorously controlled. Although randomized clinical trials, which minimize variability, are useful for assessing the efficacy of one drug versus another, they may not inform on the effects of a drug after it has been released for use in the general population.

PMS studies can also provide valuable information on the use of medical devices in the patient populations. PMS studies allow for the monitoring usage of medical device in general patient population whether the product which met it is intended purpose, safety, quality as per the requirements. Thus, factors that contribute to the need for PMS studies include a better understanding of the effects of a new medical product in larger populations in clinical practice, and changes in the regulatory approval process based on the categorization and the nature of the medical device. PMS study data helps and prove that the medical device used in patient population are doing well with patients and in the market without any incidence to confirm that the products are very safe to use continuously for a targeted population [3].

Changes are becoming mandatory in many countries where regulatory agencies are requesting additional post marketing data that would show the continued safe use in the treated population. Studies may be proposed voluntarily as a part of a marketing authorization holder's (MAH) risk-management plan (RMP) or mandated by a country regulatory authority as a post marketing commitment linked to obtaining the initial country regulatory approval [4]. Around the world each region will have their own federal requirements and guidance for post marketing commitments. Concepts involved in these studies are similar. In Europe, the development of post authorization safety study protocols is guided by the European Medicines Agency. Current article discusses about the PMS report based on MDR 2017/475. We have reviewed and addressed the published requirement of PMS as per EUMDR. Interpretations of the guideline requirements are included and applied according to the manufacturer perception.

Procedure for Conducting Product Specific Post Market Surveillance (PMS)

Post Market Surveillance (PMS) Plan and Report

For each device and/or family of devices, manufacturers will plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device. This system will be defined in the PMS Plan for each device and/or family of devices, which includes actively collecting, recording and analyzing relevant data on the quality, performance and safety of a device throughout its entire lifetime, and helps to draw the necessary conclusions to determine, implement and monitor any corrective and preventive actions. The risk method used for the PMS process is defined by the frequency of data review mandated for each class of device as defined in Table 1.

Table 1. Frequency of updates needed for medical devices

Device Classification	Frequency of initial and updates (Devices listed in Annex XVI)
Classification of the Device	**Frequency of updates**
Class I	1-year initial data evaluation with a 3-year updated review
Class IIa	1-year initial data evaluation with a 2-year updated review
Class IIb	1-year initial data evaluation with a 1-year updated review
Class III	1-year initial data evaluation with a 1-year updated review
Custom Made Devices	Per documentation referred to in Section 2 of Annex XIII.

The frequency of review can be amended as per the manufacturer's responsibility based on the availability of incidence report. However, every product PMS Plan and Report shall evaluate, as a minimum, the following: information concerning serious incidents, including information from PSURs, and field safety corrective actions; records referring to non-serious incidents and data on any undesirable side-effects, information from trend reporting; relevant technical literature, databases and/or registers, information including feedbacks and complaints, provided by users, distributors and importers; and publicly available information about similar medical devices in database.

The data gathered by the PMS system will address following: to update the benefit-risk determination and to improve the risk management, to update the design and manufacturing information, the instructions for use and the labelling[5], to update the clinical evaluation, to update the summary of safety and clinical performance, need to identify and prevent field safety corrective action, to identify and improve the usability, performance and safety of the device, when relevant to contribute to the post-market surveillance of similar devices; and to detect and report trends in accordance with Article 88.

After having all the information, technical documentation is updated accordingly. During post-market surveillance, in case of any incidence occurred there is a need for preventive or corrective action to be taken with internal procedure. Based on the severity of the occurrence competent authorities are to be informed as applicable, the notified body and or applicable economic operators. It should be addressed according to current regulatory requirements. PMS plan should include characterization and performance of the device itself and incase of any similar products existing in the market, how to assess the collected data, continuous reassessment in order to evaluate the benefit risk analysis ratio and managing the risk, effective protocol to manage PMS data collected in the field, trend reporting, communicating to the authorities and other stake holders. Post market clinical follow-up is done once the CAPA solved in the field. All information should be documented in the concerned format.

Periodic Safety Update Report

The frequency of the initial and subsequent reviews of the data for Post-Market Surveillance should be done according to the PMS Plan for each device and/or family of devices. This analysis/evaluation is based on risk of the product as it requires an increased frequency of review as the classification of the device or family of devices increases. As outlined in Table 2 the implementation of the PMS plan can result into two different types of post-market reports.The mentioned requirements are mandatory for having valid CE mark. This current regulatory requirement became effective from May 2020. NBs might ask PMS data at any time.

Source of Data Collection

Manufacturers should have Annual Overall Post-Market Surveillance evaluation at least once per year based on the classification of product. During management review meeting all the collected data and its evaluation is reviewed, as per the management vision, mission and the measurable objectives of all these data are reviewed in order to improve entire QMS which includes the trends of events. The Post Market Surveillance plan uses active and passive feedback information from production and postproduction activities already being collected for clinical assessment, for complaints, from reporting, and for various other post market activities. The main aim of these activities is to ensure the product performs according to the intended requirements using all applicable data that can be accessed. PMS Annual Plan includes: Overview/Agenda, Outstanding Issues, Department updates from marketing, finance, engineering, operations, quality , service, regulatory and clinical and other related areas. This section will address any outstanding issues from previous Post Market Surveillance for certain product or product family. Completed outstanding issues will be reviewed by the top management during the annual management review. Finance department will present overall business data during the review period. For example: Units sold, Revenue, Average Sales Price

Table 2. Different types of post-market reports.

Device classification	PSUR	Mode of submission	Frequency Update
Class I	PSUR	At request	Based on request
Class IIa	PSUR	NB assessment review	Minimum of two years once
Class IIb	PSUR	NB assessment review	Once in a year
Class IIb	PSUR	Via Euda Med for NB review	Once in a year

Class III	PSUR	Via Euda Med for NB review	Once in a year

Marketing

Marketing department will provide customer survey results, distributor feedback, and sales feedback. In the CRM database ensure gate items have been resolved, Customer/User Survey Question Topics. Surveys of customers (to include users, distributor, importers (as applicable) should be carried out to obtain informationSurveys may be done periodically for all customers with product subject to the Post Market Surveillance Plan, or when regular schedule preventive maintenance can be done. In either case, the purpose is to obtain maximum unbiased response. Surveys may be verbal, regular mail, or electronic in nature. Additional questions related to marketing or sales interests may be included.

- Confirmation of products owned-used.
- Reactions towards manufacturers supplied support materials.
- General efficacy results from use
- Ergonomics/ Human Engineering reaction
- Training adequacy
- Instruction manual adequacy
- Service adequacy
- Technical service or field support acceptability
- Issues related to suggested operational settings
- General observations regarding side effects
- Overall satisfaction
- Other clinical related questions based specific product

Engineering

Engineering department is in-charge to ensure sustaining activities of product reliability performance, and product new/improved function initiatives as well as publicly available information about similar medical devices.

Operations

Manufacturing and operation department should monitor collecting data related to operation performance.

Service

Service department shall provide data regarding on field product performance, repair data, and cost of repair/maintenance data.

Regulatory

Regulatory department shall provide information on vigilance and MDR reports during the review period for both manufacturers and direct competing product from other Medical Device companies. Regulatory department shall also provide information regarding regulatory compliance changes. For example: 510K submission, laser reports, letters to file, external approvals and reviews.

Quality

Quality department shall provide customer complaint data including non-serious incidents and any undesirable side-effects, serious incidents including data gathered from PSURs, reportable adverse event data, field safety corrective actions, monitor CAPA, Internal Audits and other related activities. The information shall also include data from trend reporting.

Clinical

Clinical department should provide Post-Market Clinical Follow-up (PMCF) or technical literature, databases and/or registers, to share with other departments regarding clinical safety and performance. Clinical assessments may also develop information useful to sales and marketing which would be an input to Post Market Surveillance. Specific post-market clinical follow-up is part of clinical assessment.

Post marketing surveillance: MHRA

PMS or pharmacovigilance in the UK is practiced in the form of the Yellow Card scheme that is jointly operated by the MHRA and the Committee of Human Medicines (CHM). The Yellow Card scheme is credited as being one of the first PV schemes aimed at mitigating ADRs. PV encompasses the objectives: (a) Monitoring the use of medicines in everyday practice with the aim to identify erstwhile unrecognized ADRs and also changes in the patterns of adverse effects. (b) Carrying out risk–benefit analysis for medicines and suggesting suitable actions, if and when necessitated. (c) Providing regular updates to healthcare professionals and patients with regard to the safe and efficacious use of medicines. Yellow card scheme is established in the year 1964.MHRA launched the Yellow Card scheme website in 2002. This website has been updated by the MHRA on a regular basis to keep up with advances in technology. In 2008, the website was redeveloped and launched, coinciding with the launch of the Patient Reporting scheme.

PMS in UK: features and aspects

Spontaneous reporting of ADRs is an integral mechanism of PV, and the Yellow Card scheme in the UK fulfils this requirement. Yellow Card reports can be submitted directly to the MHRA via post, telephone or the internet. The essential reason to establish spontaneous reporting schemes is to detect adverse reactions to new drugs as well as established drugs, as clinical trials cannot define rare but important ADRs. Although clinical trials are funded by large sums of money running into millions, companies usually fail to detect rare ADRs, as drugs will be administered to a relatively smaller population base of 2,500 volunteers, out of which only about a 100 or so will have taken the drug for a duration lasting more than 1 year [6]. Therefore, it is prudent that the MHRA functions efficiently in operating the Yellow Card scheme in

order to discern previously known ADRs and convey information about the same to the healthcare community.

Yellow card information is transferred into the MHRA database and the scientists/officials will use the data to check for the safety issues to the patients and communicate to the general population and healthcare personnel to create awareness among them about medical products and their feedback. Any adverse events related to the medical devices will be reported, MHRA published bulletin will give the latest information of medical devices. MHRA maintains data base which also include all medical product related events. Regulatory authorities ensure that all the manufacturers are complying with the requirements in order to safeguard the health of patients. Regulation of medical devices is done basically on the severity of the medical devices. Medical devices are having important role in the patient normal lives. To ensure the safety, quality and performance of the product post marketing surveillance is done to have the details of the product on the field is safe and secure [7].

Current regulation in the medical device manufacturing requirements in the guidelines and the amendment in the law will provide adequate guidance for both the manufacturers and competent authorities to addresses any area of medical devices effectively in order to have a proper outcome in medical device manufacturing and related processes. Manufacturers should have their product post marketing data and update the information in the technical documentation and coordinate with national and international competent authorities. Manufacturers should establish PMS plan in their QMS, in case of any other information of field corrective actions that also should be updated in the technical documentation [8], especially Class IIa, IIb and III medical devices are needed to submit PSUR along with benefit risk ratio, clinical follow up, volume of sales and use of the device in terms of population [9].

PMS USA

The FDA require post-market surveillance for class II and class III medical devices which falls under following criteria: device failure due serious adverse events, the device is in the body for more than a year, the life support device which is outside of facility of users. FDA will obtain PMS data from premarket setting or clinical practice. FDA ask for PMS plan which includes background, regulatory history, description, and indications, purpose of the PMS plan, PMS plan objectives and hypothesis, PMS design, patient population statistically justified sample size calculation, primary and secondary endpoint and its definitions, study criteria, unexpected ADR, and an agreement to collect unexpected adverse events, descriptions of the follow-up schedule, length, and assessment procedures, relevant data collection forms and description of data collection procedures and statistical analysis, reporting schedules for interim and final reports, interim and final data analyses, milestones/timeline elements [10].

Prior to marketing the product, clinical evaluation is done by the physician in order to release the product in market in a controlled environment. Mostly adverse event is noted only after the use of product. PMS is the integral part for the new product launching, as per the new MDR regulation concentrated only on risk-based approach [11]. In recent years, a growing number of patients have suffered from adverse events due to medical devices. To better understand the reasons especially in quality and safety and analyzed adverse event reports and recall data and constant monitoring and analysis of PMS data can provide updates on the product performance in the field. Post marketing system surveillance is analyzed qualitatively and quantitatively in terms of incidence occurrence. The analysis and evaluation is done based on the PMS plan and protocols, the monitors will monitor and address the CAPA in case any serious incidence occurred. The details are captured in the clinical dept, which includes all the details of occurrence and taken CAPA and the effective follow-up of the occurred incidence. It also includes the clinical trial which was done prior to the release of product in the market in order to prove safety, quality and intended performance of the devices.

Post-marketing surveillance (PMS) may identify rare serious incidents or adverse events due to the long-term use of a medical device, which was not captured in the pre-market process [12]. The recent regulatory revision is asking all the manufacturers to comply with the new requirements that is applicable from May 2020. Recent studies also revealed that regulatory framework emphasized on the risk assessment [13]. Data ~~c~~ollected from the marketing and clinical depts. are verified for its accuracy and quality personnel critically review the PMS data using internal checklist tools.

Post-market surveillance systems reduce both costs and demands on resources and increase product safety and performance. The PMS should be more robust in high-risk products that lead to earlier detection of potential product failures in the field. A PMS plan helps to have proactive data gathering and analysis, thus manufacturers should take a risk-based approach for clinical and medical device post-market surveillance requirement needs. FDA insists manufacturers to have PMS for high-risk products.FDA is authorized to required manufacturers to conduct PMS for certain class II and class III medical devices. Examples include infusion pumps (class II); implantable pacemakers (class III); and HIV diagnostic tests (class III). It also wishes to have monitoring period of three years or longer to comply PMS. Many manufacturers distributing CE-marked medical devices in the EU have recognized the need for PMCF, similar to FDA.

Developing a good post-market surveillance system

An experienced person should be in manufacturing units to prepare a proactive PMS system to identify sources which in turn have impact on product quality, proposing a central safety repository to assure data collection, aggregation, and analysis, revealing signals of potential issues before they occur

Post-Market Surveillance System

Medical device manufacturers can achieve a quality standard by early implementation of proactive PMS programs which in turn leads to cost of customer satisfaction [14]

CONCLUSION

Medical device manufacturers are required to maintain a PMS system for their medical devices as per EU MDR. PMS

is a systematic procedure to collect and review information on marketed medical devices. Continuous monitoring of medical device helps to identify hazards associated risks and provides prior feedback of device use among patients. PMS system collects post-market data from complaint and incident reports and failure analysis [15], while a proactive system can gain insights on a device in near-real time through electronic medical records, claims databases, literature, and even customer surveys on social media. Any unwanted incident happens during this period should be documented (PSUR) verified by the QMS process [16]. Risk severity and frequency is updated in risk management. A clinical evaluation report is updated with the gathered information. The feedback can be incorporated for design improvements.

Addressing challenges for medical device manufacturers

Medical device manufacturer gathers the information from incidents, data bases, literature, sales contacts, etc. the mentioned details will help in identifying a problem associated with the product. PMS on medical device is established based on the risk associated with the device and its intended use. Post marketing studies gives the details of performance monitoring of device efficacy, surveillance initiatives, and market acceptance initiatives. FDA is actively re-envisioning its national post-market surveillance system, with the goal of developing a life-cycle approach to product evaluation that integrates pre-market and post-market evaluations. The role of post-market research studies, particularly clinical trials enhances our understanding of medical device efficacy and safety. The broader system of evaluation, including both existing data sources and robust clinical trials addresses specific efficacy and safety objectives.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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