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Post-Marketing Surveillance and Vigilance for Medical Devices for Europe.

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ABSTRACT:

The extent of accountability for medical device manufacturers In the early stages of the European Community Directives governing medical devices, the issue of actively monitoring product performance post pre-market approval has been a subject of persistent debate. The legal framework in Europe further adds to the complexity of this matter, with frustratingly unclear guidelines. Although specific and fairly explicit obligations exist for reporting incidents to authorities through the 'vigilance system,' there remains a significant lack of clarity regarding the extent to which manufacturers should proactively investigate and comprehend such incidents., considerable attention was devoted to crafting guidelines that could aid in interpreting the requirements for reporting under the vigilance system. However, only recently has there been a shift in focus towards elucidating the expectations surrounding post-market surveillance (PMS) in a more comprehensive manner. This article delves into the intricacies of both vigilance and post-marketing surveillance (PMS) procedures, shedding light on the current guidance documents in Europe, with a primary focus on the UK. These documents aim to promote a fair and level playing field across the industry concerning vigilance and PMS practices. The article elucidates the crucial distinctions between vigilance and post-marketing surveillance. Vigilance is outlined as the systematic procedure through which manufacturers communicate adverse incidents to regulatory authorities and subsequently exchange essential incident data among themselves. On the other hand, post-marketing surveillance is described as the method by which comprehensive information on the overall performance of a medical device is gathered and analysed.

1. Introduction

During the implementation of the Medical Devices Directives [1-3] in Europe throughout the 1990s, manufacturers and competent authorities (CAs), assumed certain incident reporting responsibilities within the European Vigilance System. These obligations are explicitly outlined in the articles and annexes of the European Community (EC) Directives. Over time, as guidance materials have become more abundant, there has been an increasing awareness and understanding of these reporting requirements among relevant. [4]

Over the past few years, the UK Medical Devices Agency (MDA) has observed a notable improvement in the understanding and interpretation of vigilance standards within the industry and among fellow Competent Authorities (CAs). The amendment of the EC Vigilance Guidelines has played a clear role in enhancing consistency among CAs. Additionally, the MDA has contributed to greater uniformity by publishing several UK device-specific vigilance guidance documents that elucidate reportable events for industry.

These advice documents [5-8], which cover areas such as joint replacements, breast implants, artificial heart

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valves, and coronary stents, currently have applicability exclusively within the United Kingdom. However, there is an expectation that these guidelines will be adopted by other CAs at the European level, with any necessary amendments or modifications to ensure widespread adherence and consistency across regions.

Post-Marketing surveillance

Vigilance has long been a prominent topic of discussion at conferences and seminars, capturing significant attention. However, only recently has there been a growing recognition that vigilance constitutes just one facet of the broader post-marketing surveillance needed mandated by the EC Directives for manufacturers. As outlined in the annexes of the EC Directives, manufacturers are mandated to 'establish and maintain an organized procedure for reviewing experiences are gaining by the devices in the post production phase.' This requirement goes beyond the singular duty of notifying Competent Authorities (CAs) about vigilance cases; instead, it encompasses a systematic approach to continuously assess and update insights garnered from devices in the post-production phase. The experience of the UK Medical Devices Agency (MDA) indicates a common misunderstanding and undervaluation of this broader PMS requirement within the industry.

It is crucial to recognize that while the duty to report vigilance cases to CAs is part of PMS, it does not encapsulate the entirety of the manufacturer's commitment to ongoing surveillance and analysis of post-market device performance.

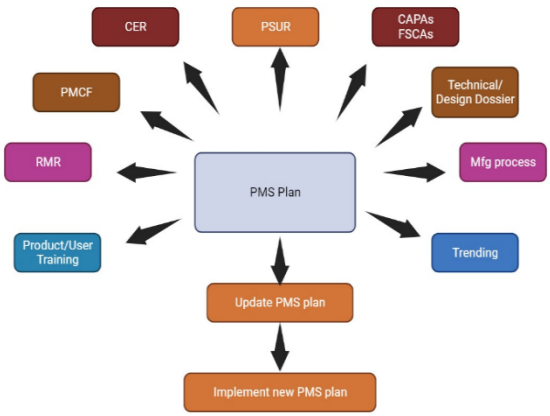

Fig.1. Post marketing surveillance process

As yet by the guidance dedicated to PMS than to vigilance. To address this need last years the EC notified bodies expert groups produced some generic device guidance to expand upon text PMS process. .[9]

Why we need post -marketing evidence

Consequently, maintaining continuous post-marketing surveillance of vaccine safety is imperative to identify and assess potentially rare adverse events. This on going monitoring serves a crucial role in enabling the re-assessment of the benefit-risk profile of vaccines. While spontaneous reporting of adverse events remains a fundamental aspect of most post-marketing safety monitoring systems, the expanding accessibility of electronic healthcare data has introduced new possibilities for safety surveillance [10,12].

Post Marketing Surveillance one part of quality system

Currently, there is relatively less guidance available specifically dedicated to Post-Marketing Surveillance (PMS) compared to vigilance. Recognizing this gap, the Notified Bodies Experts Group took a step last year by producing generic devices for guidance to elaborate on the content within the EC protocols [9] Therefore, for comprehensive guidance on PMS, it is crucial to acknowledge that PMS is an integral part of any complete quality system, as illustrated in Figure 2. It is represents the of the product development lifecycle. Given the cyclical nature of this process, PMS also plays a pivotal role in providing essential input to the initial stage of product development, known as design control. Several standards are dedicated to interpreting the quality system standards such as ISO 9000 and EN46001 [13], offering insights into the requirements for PMS. One noteworthy standard is ISO 9000-4 [14], which emphasizes feedback "permit the analysis on a continuing basis, of the degree to which the product satisfies customer requirements or expectations on quality, including safety and dependability." Additionally, EN 50103:1995 [15] references the crucial concept of these references detection have performing identify potential efficiencies .

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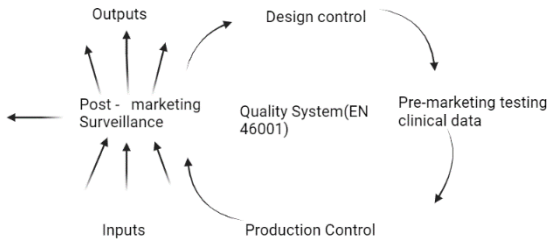

Fig.2 Post – Marketing surveillance one part of quality system

The enforcement of harmonized legislation on medical devices falls under the jurisdiction of authorities in EU countries. The Medical Devices Directives outline specific procedures that national authorities must adhere to when determining the safety of a medical device, including the potential need for withdrawal from the market using the 'safeguard clause.' This clause is invoked when a medical device is deemed unsafe. Similarly, procedures are established for cases where a CE marking is either unduly affixed to a device or missing, indicating a 'wrongly affixed CE marking.' When necessary, the European Commission ensures the consistent application of these procedures across the EU. Furthermore, countries have the authority to establish health-based requirements pertaining to the withdrawal or introduction of a specific product or group of products to the market through 'particular health monitoring measures.' Ideally, these measure should be implemented uniformly as EU-wide measures [16].

2. The Vigilance system

By functioning as a proactive surveillance mechanism, the Medical Device Vigilance System facilitates the timely identification of any emerging issues or safety risks tied to the use of medical devices. This early detection enables prompt intervention and corrective measures to be implemented, preventing the recurrence of incidents that could compromise the health and well-being of patients, as well as the safety of healthcare professionals and other users.

The Directives specify that adverse incidents must undergo evaluation, and if deemed necessary, information should be disseminated in the form of a National Competent Authority Report (NCAR). The purpose of this process is to prevent the recurrence of such incidents by implementing appropriate field safety corrective actions. The provisions regarding vigilance in the Medical Devices Directives are complemented by general guidelines on vigilance. These guidelines aim to facilitate and harmonize the implementation of EU Directives, covering various aspects such as performance issues or conducting a comprehensive incident investigation. Subsequently, a final vigilance report is submitted to the Competent Authority (CA), confirming the company's conclusions. This process is essential for managing risks associated with medical devices and involves collaboration between manufacturers and competent authorities [16]. The second phase of Post-Marketing Surveillance (PMS) involves evaluating data on device performance and determining the necessity for any form of corrective action. Within this phase, reportable vigilance cases are identified, and an initial report is submitted to the Competent Authority (CA). This stage encompasses a comprehensive analysis. During the same period, the MDA introduced the first UK device-specific guidance document on post-marketing surveillance. This document outlines the minimum expectations for the ongoing monitoring of the performance of joint replacements following market approval. It emphasizes the importance of continuing the follow-up of patients involved in any pre-marketing clinical investigations. The guidance also underscores the value of structured postmarketing clinical studies, emphasizing that data collection within such studies should adhere to standards similar to those applied in pre-marketing trials.

Furthermore, the document recognizes the role of implant registries in tracking devices and their performance. It stresses the significance of establishing effective communication links with the medical profession to obtain expert and up-to-date feedback [17].

i. Eudamed2 - European Databank on Medical Devices

Eudamed2 is a crucial platform for managing data on medical devices in Europe. It plays a vital role under the relevant directive, handling various types of

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information. If you have anything feel ask to free specific questions [18].

Eudamed2 is a key platform in Europe for handling information about medical devices. It's like an online hub that securely manages data under specific guidelines. It deals with things like registering manufacturers, representatives, and devices, as well as keeping track of certificates and clinical investigations. This platform is crucial for sharing information between authorities and the Commission, all while keeping everything confidential. It's not accessible to the public to protect sensitive data. Since May 2011, it's been mandatory to use Eudamed2, strengthening its role in surveillance, transparency, and following standardized guidelines. Medical devices, including those for in-vitro diagnostics, are really important for public health. The vigilance system makes sure they're safe, effective, and innovative by regulating and monitoring them

.• Manufacturers and users submitting vigilance reports (incidents and field safety corrective actions) to the relevant competent authorities (the HPRA in Ireland);

- The scrutiny of reports by competent authorities, as outlined in [19], recognizes the crucial role of implant registries in monitoring the performance of medical devices. It underscores the significance of establishing effective communication channels with the medical community togather expert and current feedback. This acknowledgment highlights the importance of fostering strong connections with healthcare professionals, facilitating a continuous exchange of information.
- It seems like you're explaining the importance of sharing information to prevent future issues and minimize the impact of ongoing problems. Additionally, you're highlighting how actions such as updating, modifying, or removing devices from the market can contribute to these efforts. Here's a refined version in your own language. The idea here is all about sharing crucial information to prevent similar incidents from happening again or, when necessary, to reduce the severity of ongoing issues. In simpler terms, it's about passing on important details to avoid future problems or make existing problems less severe. This process involves actions like updating, modifying, or even removing a device from the market when it becomes necessary to do so [20]. It's worth noting that the legal presence of most medical devices on the market is tied to the CE marking. However, there are exceptions to this rule. Devices that are custom-made and those involved in clinical trials are not obligated to carry the CE marking. In the context of active implanted medical devices, particularly those powered by electricity, compliance is mandated with the requirements stipulated in the Active Implantable Medical Devices Directive. As a result, the Electromagnetic Compatibility Regulations (EMC) (SI 1992 number 2372) derived from Directive 89/336/EEC are no longer applicable. This shift is grounded in the principle that the Active Implantable Medical Devices Directive serves as a more specific and relevant regulation for such devices.

Concerning non-implanted electro-medical devices during the transitional period of Directive 93/42/EEC, there are multiple options available for meeting the legal requirements, as detailed in [21]. This regulatory landscape underscores the complexity of the medical devices sector and the necessity for manufacturers to stay abreast of evolving directives, ensuring that their products comply with the appropriate and updated regulations within specified timeframes [21].

Absolutely! You're highlighting the flexibility that companies have in designing their Post-Marketing Surveillance (PMS) systems, emphasizing that while minimum requirements for each device type must be met, specific details in the guidance documents are not overly prescriptive. This allows companies to tailor their systems to meet their unique needs. A key point is the evolving emphasis on distinguishing between PMS and vigilance by regulatory authorities. PMS is described as more than just a reactive response to issues; it involves a proactive approach to gather information that could potentially lead to vigilance reports. Importantly, PMS extends beyond regulatory compliance, serving broader company objectives. Crucially, PMS is portrayed not solely as a means to address negative aspects but also as a valuable mechanism for manufacturers to receive positive feedback performances. Gathering insights for potential product is another product increasing aspect. While regulatory authorities may not prioritize these positive elements, they play a crucial role in ensuring the ongoing market success of the product. In essence, PMS

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is depicted as a comprehensive system that contributes not only to regulatory compliance but also to continuous improvement and innovation, showcasing its significance in the broader context of a company's success.

ii. Corrective versus preventive actions:

In the case of identified corrective and/or preventive actions, they need to be reported to the competent authorities concerned and, if applicable, to the notified body. Actively and systematically collecting data means that one should be proactive and not reactive, meaning it is always better to prevent than correct – which saves both time and money. Preventive actions are always preferred over corrective actions, and preventive actions can only be taken if you have a proactive PMS system since reactive PMS systems would normally only result in corrective actions. The PMS data shall also be used to review and potentially update the benefit-risk determination and improve the risk management system, to update the design and manufacturing information, as well as the instructions for use and labelling .[22]

3.Periodic safety update report (PSUR)

Certainly! You're discussing the requirement for manufacturers of class IIa, class IIb, and class III devices to prepare a Periodic Safety Update Report (PSUR) for each device. Here's a refined version in your own language: Manufacturers of class IIa, class IIb, and class III devices are obligated to create a Periodic Safety Update Report (PSUR) for each device. This report encompasses a summary of results and conclusions derived from the analysis of post-market surveillance data collected through the post-market surveillance plan outlined in Article 84. The PSUR also includes a rationale and description of any preventive and corrective actions taken.Over the device's entire lifespan, the PSUR must include:

(a) Conclusions drawn from the benefit-risk determination.

(b) Principal findings from the Post-Market Clinical Follow-up (PMCF).

(c) The device's sales volume, along with an estimated evaluation of the size and other characteristics of the population using the device, where practicable. This comprehensive reporting framework ensures a continuous evaluation of the device's performance, safety, and efficacy, making a significant contribution to regulatory compliance and, most importantly, patient safety. The frequency of device usage is a key consideration in this ongoing assessment. Manufacturers of class IIb and class III devices are mandated to update the Periodic Safety Update Report (PSUR) at least annually. This report, except in the case of custom-made devices, becomes an integral part of the technical documentation as specified in Annexes II and III. Similarly, manufacturers of class IIa devices are required to update the PSUR when necessary and at least every two years, with the PSUR being part of the technical documentation as specified in Annexes II and III, except for custom-made devices, where it is included in the documentation referred to in Section 2 of Annex XIII.

For class III devices or implantable devices, manufacturers must submit PSURs through the electronic system outlined in Article 92 to the notified body engaged in the conformity assessment, as per Article 5. The notified body reviews the report, appending its evaluation to the electronic system along with details of any actions taken. These PSURs and the evaluations by the notified body are then made accessible to competent authorities through the electronic system.

In the case of devices other than those mentioned in the preceding paragraph, manufacturers are required to provide PSURs to the notified body involved in the conformity assessment and, upon request, to competent authorities [23].

they'll talk about things like making it easier to handle complaints, quickly noticing when something goes wrong, dealing with field corrective actions, managing when devices are used differently than intended, dealing with feedback and surveys from patients, and making sure everything follows the rules. It's basically a way to improve products and processes in the medical field. [24]

Certainly! In your own language, you're expressing that regulatory authorities permit medical devices to be introduced to the market when there is sufficient data affirming the reasonable assurance that the proposed

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device is safe and effective. This data typically includes prospective premarket information, which is obtained by utilizing ideal devices under optimal conditions [25].

Monitoring medical devices goes beyond just managing incidents; it involves a proactive strategy to keep an eye on the balance between the benefits and risks of a product throughout its entire life cycle. The significance of Post-Market Surveillance (PMS) has become more pronounced with the implementation of the Medical Devices Regulation (MDR). This article aims to give a broad look at the basic requirements for PMS, covering different phases and formats. The discussion considers the relevant rules, guidance from the Medical Device Coordination Group, and applicable standards [26].

- **Surveillance planning**

Defining measurable indicators and establishing thresholds associated with the intended objectives [27]. Targeted Data Details: Specification of the nature of data, including details on sampling, and determining the frequency of data collection. Tools In pharmacovigilance and AEFI surveillance [28].

- **Changes to EMA guidance**

Not too long ago, the EMA (European Medicines Agency) asked makers of seasonal flu vaccines to do small studies with at least 50 people in two age groups: 18 to 60 years old and over 60 years old [29].

As part of the 'Good Pharmacovigilance Practices,' the EMA suggests that the name of the product and the batch number should be noted at every step, from when it's made until it's given to someone. They really stress the importance of keeping track of this information, even if there are differences in how things are done in different places or with different healthcare systems [30].

- **Conclusions**

The fact that the guidance documents don't provide specific details on the logistics and structure of an ideal Post-Marketing Surveillance (PMS) system suggests that companies have the freedom to customize their systems to fit their unique needs. They must, of course, still meet the minimum requirements for each device type. Interestingly, regulatory authorities are now stressing the difference between PMS and vigilance. PMS is not just about reacting to issues; it's a proactive approach to gather information that could lead to vigilance reports. Moreover, its scope extends beyond mere regulatory compliance to encompass broader company objectives. Crucially, PMS isn't solely focused on addressing problems. It's a valuable tool for manufacturers to receive positive feedback on how well their devices are performing and to gather insights for potential improvements. While regulatory authorities might not prioritize these positive aspects, they are pivotal in ensuring the ongoing success of the product in the market. In essence, PMS is a comprehensive system that contributes not only to regulatory compliance but also to continuous improvement and innovation in the industry.

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