

Risk management system and risk minimization measures as crucial part in implementation of good pharmacovigilance practice

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Introduction

Each drug is authorized for a specific indication(s) based on a positive risk-benefit ratio confirmed in the clinical phase of drug development. It is generally expected in post marketing period each drug to be associated with adverse reactions that vary in severity, likelihood of occurrence, effect on different patients, and impact on public health. All adverse reactions and risks may not be identified during the initial application for marketing authorization and some will be identified and characterized in the post marketing period.

In EMA the pharmaceutical companies have to submit risk management plan while applying for marketing authorization. In addition, for medicines registered by national procedure, national competent authorities in EU may request RMP to be submitted whenever there is a suspicion of a benefit-risk balance of the drug. The RMP is a dynamic document that is continuously modified and updated over the drug life cycle as more information on the drug's safety profile is obtained that influence its safety profile (GVP, Risk management system, 2017). FDA has had many regulatory initiatives that could be classified as forms of risk management procedures, such as classification of some OTC drugs in prescription drugs, since it ensures their

safe use only under supervision of a HCPs. Prior to 2007, the pharmaceutical companies in the United States have been submitting specific safety programs: Risk Management Programs (RMPs) or Risk Minimization Action Plans (RiskMAPs) for a limited number of drugs with significant therapeutic benefit, while starting from 2007 the companies are submitting Risk Evaluation and Mitigation Strategy (REMS) (FDA, 2018).

Materials and Methods

Relevant European, US and Macedonian legislations have been reviewed, in particular, Directive 2010/84/EU, Regulative (EU) 1235/2010, rulebooks, as well as PubMed, Medline and other relevant web sites for articles with empirical analysis, are evaluating the impact of European and non-European regulatory activities.

Results and Discussion

According to EMA and FDA legislation MAHs should have established appropriate risk management system and should continuously monitor the safety profile of the medicinal product by monitoring the pharmacovigilance data in order to determine whether there are new risks, or changes

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in the risks or risk-benefit ratio of the drugs in order to update the risk management system and RMP accordingly. The safety profile of the medicinal product should be constantly monitored and presented in the updated Periodic Safety Reports (PSUR). Although PSUR is a retrospective, integrated post-marketing document and RMP is prospective pre- or post-marketing document, both are complementary documents (GVP, Risk management system, 2017).

The RMP consists information for the drug's safety profile, information on how the risks associated with the drug use will be prevented or minimized in patients, study plans and other activities to provide more information on the safety and efficacy of the drug, and to determine the effectiveness of the implemented risk minimization measures (GVP, Risk management system, 2017).

On the other hand, REMS consists information that should be transmitted and / or required activities to be taken by healthcare professionals, pharmacists, patients who prescribe, dispense or use medication. Together, these activities provide a secure strategy in effective, safe and rational drug use (FDA, 2018).

In some cases, both documents, RMP and REMS, include additional requirements such as clinical activities that HCPs may need to perform prior to prescribe or dispense the drug to the patient. Such example is severe allergic reactions immediately after administration of the drug, so risk minimization measures are needed to ensure that the drug is administered only in healthcare facilities with HCPs trained to deal with severe allergic reactions or the need of lab testing and checking of results before administration of the drug. Risk minimization measures may include education of HCPs for certain patient groups that are more likely to experience an adverse event and thus avoiding prescribing the drug in these patients, or the need for patients cards with important information for the drug (FDA, 2018; GVP, Risk management system, 2017).

Risk minimization strategies should be well evaluated from the time of drug development. The knowledge of the constituents or class of the drug in the period of drug development is sufficient for prediction of the post-marketing risk minimization activities. The use of these strategies can significantly reduce the post-marketing risk of the drug (Dieck and Sharrar, 2013; Mollah, et al., 2014).

There are number of risk minimization activities that can be introduced, starting from packaging design, examination of educational material, to more

complex activities such as safety studies. These pre-marketing activities will not help to avoid the occurrence of unknown, serious risks identified in the post-marketing period, but could help the manufacturer to responds quickly and effectively to unexpected safety-related events and to properly manage the identified risks (Dieck and Sharrar, 2013).

Conclusion

In N. Macedonia all risk minimization measures are approved by MALMED through the Committee for safety and advertising since the current Law does not contain sufficient information regarding the risk management. These local legal documents should be harmonized with regulation and rulebooks for good pharmacovigilance practice approved and implemented by EMA.

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