Risk management strategies and implementation of risk minimization measures for medicinal products

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Introduction

The medicinal product can be authorized for specific indication(s) only if the positive benefit/risk balance has been confirmed in the clinical phase of the drug development. However, not all adverse reactions and risks will be identified during the initial application for marketing authorization, and some will be identified and characterized in the post-marketing period, and it is expected the adverse reactions to vary in severity, likelihood of occurrence, effects on individual patients, and public health impact.

The risk management is not a new concept, there have been many regulatory initiatives by EMA and FDA classified as forms of risk management, such as regulatory approval process, change of the legal status of some OTC drugs in prescription drugs, and inclusion of product information for patients.

In the centralized procedures for obtaining marketing authorizations in EU, the pharmaceutical companies are submitting Risk Management Plan (RMP) to EMA. 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. (GVP, Module V, 2017). The pharmaceutical companies in US were 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 since 2007 the companies are submitting Risk Evaluation and Mitigation Strategy (REMS) (FDA, 2021).

Materials and methods

Relevant EU, US and Macedonian legislations have been reviewed, in general, the Directive 2010/84/EU, Regulative (EU) 1235/2010, FD&C Act, guidelines, as well as PubMed, Medline and other relevant websites with articles evaluating the impact of EU and non-EU regulatory requirements and activities.

Results and discussion

The marketing authorization applicants/holders should have established appropriate risk management system and should continuously monitor and update the safety profile of the medicinal product by monitoring the pharmacovigilance data in order to determine whether there are new risks, or changes in the risks or benefit/risk balance of the drugs, and to update the risk management system and RMP accordingly. As part of the continuous monitoring and risks assessment, the safety signals are the first signs for possible relationship between the adverse event and the drug. (GVP, Module V, 2017).

The risk minimization strategies include information that should be distributed and/or required activities to be taken by HCPs, pharmacists, patients who prescribe, dispense or use the medicinal products (FDA, 2021).

The RMP consists information for the drug's safety profile (including important identified and potential risks and missing information), planned pharmacovigilance activities, information on how the risks associated with the drug use will be prevented or minimized, 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, Module V, 2017).

While submission of RMP is required for all medicinal products approved by EMA, there are six factors that contribute in FDA's determination of REMS submission, which include the seriousness of any known or potential adverse events and their incidence, anticipated benefit, the seriousness of the disease or condition treated, whether the drug is a new molecule, expected or actual duration of the treatment, and estimated population size likely to use the drug (FD&C Act, 2022).

The routine risk minimization measures include product information, pack size and legal status of the product and are applicable for all medicinal products. Some product information is considered as additional tools for risk minimization, such us medication guides required by FDA. The additional risk minimization measures (aRMMs) may include communication plan (e.g., educational programs, DHPC, training programs), controlled access programs and other risk minimization measures such as controlled distribution system, pregnancy prevention programs, and registries. Examples of aRMMs include activities that HCPs may need to perform prior to prescribe or dispense the drug, such as lab testing before administration of the drug, appropriate selection of patients, education of HCPs for certain patient groups that are more likely to experience an adverse event and thus avoiding prescribing the drug to these patients. Other examples may include administration of the drug only in healthcare settings by HCPs trained to deal with severe allergic reactions, certain monitoring during and/or after the treatment or the need for patients cards with important product information (GVP, Module XVI, 2017; FD&C Act, 2022; FDA, 2021; CIOMS IX, 2014).

Risk minimization strategies should be well evaluated at the time of drug development, in order the associated risks in the post-marketing period to be well characterized and minimized. These pre-marketing strategies 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 (GVP, Module V, 2017; Dieck and Sharrar, 2013).

The companies that are able to establish an organizational structure with superior communication abilities, have adequate expertise and funding, and appropriate records, will be able to develop and implement more efficient and high-quality risk minimization programs (Morrato and Smith, 2015).

The MAHs and regulatory authorities are partners in determining the need and content of the risk minimization strategy. Careful distribution planning and stakeholders contribution (such as patients, caregivers, HCPs, pharmacists) are essential to ensure risk minimization measures effectiveness (CIOMS IX, 2014).

Conclusion

Although MALMED, as a Competent Authority, is following the GVP requirements and approves the risk minimization measures through the Committee for safety and advertising, the current legislation in N. Macedonia contains limited information regarding risk management strategies. Therefore, harmonization of the local legislation with regulations and GVP guidelines implemented in EU is absolutely necessary.

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