

The legal and regulatory framework for vaccine pharmacovigilance

Ankica Gestakovska^{1*}, Brankica Moskova², Zoran Sterjev³, Aleksandra Grozdanova³, Ljubica Suturkova³, Aleksandra Kapedanovska Nestorovska³, Zorica Naumovska³

¹Quality Control Department, Replek Farm LTD, Kozle 155, 1000 Skopje, N. Macedonia

²Drug Safety Associate IQVIA, 11 Oktomvri, 7500 Prilep, N. Macedonia

³Faculty of Pharmacy, Ss. Cyril and Methodius University, Mother Theresa 47, 1000 Skopje, N. Macedonia

Introduction

Vaccine Pharmacovigilance is defined by the CIOMS/WHO Vaccine Pharmacovigilance Working Group as the science and activities related to detecting, evaluating, understanding and communicating adverse events following immunization (AEFI) and other issues related to vaccines or immunization and preventing vaccination or vaccine side effects (CIOMS, 2018).

Well established pharmacovigilance system enables early detection, an appropriate and timely response to AEFIs, minimization of the negative effects on the public health, and reduction of the potential negative impact on immunization in the population. Continuous risk-benefit assessment and risk management are an integral part of the pharmacovigilance monitoring of the vaccines. The legal framework for vaccine surveillance during the clinical phase of vaccine development and post-marketing period is essential for the implementation of good pharmacovigilance practice on a global and national level. This system should empower the public trust in the healthcare system to obtain sufficient vaccination especially for preventable diseases and improve public health nationally and globally (Di Pasquale, 2016; EMA, GVP, 2013).

Materials and methods

Relevant European, American and Macedonian legislation was 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, evaluating the impact of European and non-European regulatory activities.

Results and discussion

The vaccine supplying process is established and regulated system by national competent authorities and regularly assessed by WHO. In the process of pharmacovigilance system assessment and AEFI monitoring, seven indicators are defined and six of them are predominantly important. Licensing, marketing authorization, and pharmacovigilance of vaccines are mandatory for all countries, irrespectively if they produce vaccines or not. Also, the WHO recommends that all countries that do not produce vaccines, however, must define minimum specifications for the vaccines they use. A system of post-marketing surveillance should be established to detect vaccine efficacy or safety problems. In all countries, AEFIs should be monitored, reported and investigated by national competent authorities. Also, NCA must create a user-friendly and appropriate

* ankicagestak@yahoo.com

monitoring system of AEFIs. Additionally, a close and clear communication and information exchange system should be established among the NCA and all concerned stakeholders (Fulton, 2015; Global vaccine safety initiative, WHO 2018).

Marketing authorization, distribution, and vaccines pharmacovigilance are strictly regulated in the Republic of North Macedonia. In line with EU legislation, the national competent authority MALMED enables the controlled release of each vaccine lot after certificate assessment and inspection supervision. It has the main role in ensuring the implementation of good distribution practice procedures. An effective immunization surveillance system requires the involvement of health professionals at all levels of the immunization program. Detecting and reporting of AEFI is a responsibility of all healthcare professionals in outpatients, clinics and vaccination sites. Health personnel must have adequate training for providing proper immunization, detecting, and reporting of potential AEFIs (EMA, GVP, 2013; Mehta et al., 2000).

All detected AEFI in the Republic of North Macedonia should be reported to MALMED and the Institute of public health. Since 2018, the Republic of North Macedonia has established an electronic system for reporting adverse drug/vaccine events to enable better accessibility for health care professionals (HCPs) and patients. All collected AEFI data has a strictly defined timeline submission to the Uppsala Monitoring Center (UMC) in E2BR3 format, depending on the seriousness of the event. All reported AEFIs are assessed on the national level. A proper communication system is established for all stakeholders to increase the early detection of signals and the implementation of risk minimization or corrective measures. Only 5 AEFI cases were reported in 2017, 7 in 2018 and all of them were expected non-serious reactions. In 2019, during the measles epidemic in the Republic of North Macedonia, over 42000 MRP vaccines were given to the population. The vaccination process ended up with only 17 AEFI reported, among which only 11 were associated with the MRP vaccine. All the reported AEFI were non-serious expected events according to information listed in approved vaccines SmPCs.

As we evaluate the available data from the competent authorities, it could be noticed that the Republic of North Macedonia is facing a big problem in reporting ADRs as well as AEFIs. The small number of reported events doesn't confirm

their absence. Uncontrary, it points out that an additional educational program should be initiated to train the HCPs for detection, reporting, and evaluation of adverse events and raise the awareness for the importance of good pharmacovigilance system in our country.

Conclusion

Establishing an appropriate legal and regulatory framework and complete harmonization of national regulations with EU legislation for vaccine pharmacovigilance is inevitable. This should be sound ground for improved continuous monitoring of vaccine efficacy and safety, as well as identification of potential safety signals, conduction of risk minimization measures and better public health in the Republic of North Macedonia.

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