Macedonian Pharmaceutical Bulletin, 68 (Suppl 1) 501 - 502 (2022)
Online ISSN 1857 - 8969
DOI:10.33320/maced.pharm.bull.2022.68.03.241
Short communication

Regulatory requirements for detection and management of safety signals in pharmacovigilance

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Introduction

Well established pharmacovigilance plays pivotal role in communicating new and accurate scientifically based information for quality, efficacy and safety of marketed drugs in timely manner and guarantees the public health. Detecting unknown risks related to drugs on the market is important for ensuring optimal patient care and reducing the health costs caused by treating adverse drug reactions. Large data bases of individual case reports remain the primary source of information where automated effective statistical analyzes are performed on timely manner in order to identify drug safety signals. Information from individual case reports are communicated among healthcare professionals, pharmaceutical industry and regulators. The safety profile of the drug is constantly evolving through evaluation of new information obtained submitted individual case reports, case studies, aggregated data from active surveillance systems or studies, scientific literature information or other data sources. These data bases are pivotal in the process of detecting potential safety signals by pharmacovigilance professionals. In such manner new risks associated with an active substance or a medicinal product are identified or some known risks are changing, resulting in new recommendations, decisions, communications and tracking. When safety concern is identified, all individual case reports as well as cumulative and summary reports are assessed followed by signal validation, signal confirmation, signal analysis prioritization, signal assessment. These process results in recommendation for additional action or some other regulatory decisions. Causality assessment of identified risks and medical product is one of the major challenges of pharmacovigilance. All important safety information are communicated among healthcare professionals, pharmaceutical industry and other stakeholders (eg. clinical trial participants, researchers, consumers, etc.) in order to ensure the safe use of medicines. Decent implementation of signal management and sharing of safety information for medicines are ensuring the positive benefit/risk ratio of marketed medical products. This article aims to evaluate the actual EU legislation for signal management as the basis for improvement of pharmacovigilance regulation in the Republic of North Macedonia.

Materials and methods

The European and Macedonian legislation were reviewed, with emphasis on Directive 2010/83/EU and 2010/84/EU, relevant ICH and EMA guidelines, as well as the Law on medicine and medical devices and the Rulebook for ADR reporting in North Macedonia.

Results and discussion

During the clinical trials, the detection of ADR is limited due to targeted group of volunteers in highly controlled settings. The safety profile of the drugs is defined in the post marketing period when rare ADRs, are identified when the drugs are used in larger population groups, in specific patient groups, such patients with comorbidities, concomitant drugs or supplements treatment, pediatric or geriatric population, as well as in pregnant and breastfeeding woman. The most commonly utilized source for signal detection are the databases with spontaneous repors provided by patients or health-care workers. Additionally, with drugs novel approaches emerge such as, case control, cohort studies as well real-world data evidence. The confirmed signals are then communicated with all concerned parties, such regulatory

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authorities, pharmaceutical industry, with the healthcare workers as well as patients and consumers.

Effective post-marketing monitoring, especially spontaneous reporting of adverse drug reactions, is the primary source of information on effective pharmacovigilance and identification of new or rare adverse reactions and determination of the true frequency of adverse drug reactions. By providing a good system for pharmacovigilance, it is possible to promote and protect public health and minimize the risk of adverse drug reactions, ie the benefit-risk ratio of approved drugs is optimized.

All identified risks observed in the period of clinical trials are stated and evaluated in the risk management plans (RMP) for the drugs. Risk management plans are submitted in the procedure of authorization and risk minimization measures are well documented and planned according to identified risk during the clinical development and postmarking period of drug cycle. This documentation is constantly updated in line with all potential and identified new, ongoing or closed signals, as well as missing information for the drug and are crucial in the process of continuous evaluation or risk/benefit ratio of the drugs on market. Pharmacovigilance systems should ensure proactive monitoring of all approved drugs throughout their life cycle and use in day-to-day clinical practice. Through the processes of detection and signal management as basic activities in pharmacovigilance, new information is provided on the safety of drugs for use in the general population and the increase of the benefit and the reduction of the risk from the use of the drugs are provided. Early detection of safety signals is the basis for taking appropriate measures to minimize the risk, identify risky outbreaks of patients and limit the use of drugs in them, which increases the benefits. All identified, open, current and closed signals, as well as potential risks and missing information about medicines, are always listed in the Periodic Safety Update Reports (PSURs) submitted to regulators at strictly defined intervals, and provides an extension of the shelf life of the drug on the market.

Conlusion

There is a growing need to establish effective pharmacovigilance system and good electronic health records that will contribute to the detection and evaluation of signals on national and global level. Good collaboration between all stake holders will help in taking the regulatory actions in timely manner in order to prevent the public health and enable safe use of drugs.

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