SHAREme.

Scientific Hub of Applied Research in Emerging Medical science & technology

Published: 27.03.2026

check for updates

Review Article

Evolving Risk Management Plans (RMPs) in Global Pharmacovigilance: Challenges and Future Perspectives

Akhila Ajith[1], Thota Lakshmi[2*], HB Allankritha Sri[3], Nandini Penchala[4], Sayanolla Archana[5], A Dhanush Kumar[6]

[1, 2, 3, 4, 5, 6]Doctor of Pharmacy, Department of Pharmacy Practice, Malla Reddy College of Pharmacy, Hyderabad, Telangana, India

*Author for correspondence: Thota Lakshmi
Email ID: lakshmithota5678@gmail.com

Abstract

Pharmacovigilance plays a crucial role in ensuring the safety of medicinal products throughout their lifecycle. With the growing complexity of pharmaceutical development and the increasing global use of medications, regulatory authorities have emphasized proactive strategies for identifying and managing drug-related risks. Risk Management Plans (RMPs) have emerged as essential tools in modern pharmacovigilance systems, providing structured approaches for identifying potential safety concerns, monitoring adverse drug reactions, and implementing risk minimization measures. Over the past two decades, regulatory frameworks such as the European Union Risk Management Plan (EU-RMP) and the United States Food and Drug Administration's Risk Evaluation and Mitigation Strategies (REMS) have significantly strengthened global drug safety monitoring. Despite these advancements, several challenges remain in the effective implementation of RMPs, including variations in regulatory requirements across regions, limitations in real-world safety data, underreporting of adverse drug reactions, and difficulties in evaluating the effectiveness of risk minimization strategies. Additionally, the increasing globalization of pharmaceutical markets has created a need for greater harmonization of pharmacovigilance practices among regulatory authorities. Emerging technologies such as artificial intelligence, big data analytics, and real-world evidence are expected to play an important role in improving signal detection and strengthening risk management systems. This review discusses the evolution of Risk Management Plans in global pharmacovigilance, outlines their key components and regulatory frameworks, examines the major challenges associated with their implementation, and highlights future perspectives aimed at enhancing drug safety monitoring and patient protection.

Keywords: Risk Management Plan, Pharmacovigilance, Drug Safety, Risk Minimization, REMS, Regulatory Affairs

Introduction

Pharmacovigilance plays a critical role in ensuring the safety and effectiveness of medicinal products throughout their lifecycle. It involves the science and activities related to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) and other drug-related problems after a medicine is marketed.

Although pre-marketing clinical trials provide essential information on the safety and efficacy of drugs, they are conducted on limited patient populations and for relatively short durations. As a result, rare or long-term adverse effects may only become apparent after widespread use of the medicine in real-world clinical settings. This highlights the importance of robust post-marketing safety monitoring systems and structured pharmacovigilance strategies (1,2).

Risk Management Plans (RMPs) have emerged as a fundamental component of modern pharmacovigilance systems. An RMP is a structured document submitted to regulatory authorities that describes the risk management system for a medicinal product. It outlines the known and potential safety concerns associated with a drug and proposes strategies for monitoring, preventing, or minimizing those risks. The primary objective of an RMP is to ensure that the benefits of a medicinal product outweigh its risks during both the pre-authorization and post-authorization phases (3).

The concept of risk management in pharmacovigilance has evolved significantly over the past two decades. Regulatory authorities worldwide have increasingly emphasized proactive risk identification and management rather than relying solely on passive adverse event reporting systems. The European Medicines Agency (EMA) introduced formal Risk Management Plan requirements in 2005 as part of the European Union pharmacovigilance legislation. Similarly, the United States Food and Drug Administration (FDA) implemented the Risk Evaluation and Mitigation Strategies (REMS) program to ensure that certain medications with serious safety concerns are used appropriately and safely (4,5).

Risk Management Plans typically consist of three key components: the **safety specification**, the **pharmacovigilance plan**, and **risk minimization measures**. The safety specification identifies important identified risks, potential risks, and missing information related to the medicinal product. The pharmacovigilance plan describes activities designed to further characterize and monitor these risks, such as post-authorization safety studies (PASS) and enhanced safety surveillance. Risk minimization measures include both routine and additional interventions aimed at reducing the likelihood or severity of adverse events associated with the drug (6).

With the increasing globalization of pharmaceutical development and regulatory oversight, risk management strategies have become more complex. Pharmaceutical companies often need to develop and maintain risk management plans that satisfy the requirements of multiple regulatory authorities across different regions. Variations in regulatory expectations, differences in pharmacovigilance infrastructure, and challenges related to data integration and communication can complicate the implementation of global risk management programs (7,8).

Furthermore, the growing availability of real-world data from electronic health records, patient registries, and large healthcare databases has created new opportunities for improving pharmacovigilance and risk management practices. Advanced data analytics, artificial intelligence, and machine learning technologies are increasingly being explored to enhance signal detection, identify safety trends earlier, and improve the effectiveness of risk minimization strategies (9,10).

Despite significant progress in pharmacovigilance systems, several challenges remain in the effective implementation of Risk Management Plans. These include limited access to high-quality real-world evidence, difficulties in evaluating the effectiveness of risk minimization measures, regulatory inconsistencies across regions, and resource constraints in pharmacovigilance systems. Addressing these challenges is essential for strengthening global drug safety monitoring and ensuring optimal patient protection (11).

Therefore, this review aims to examine the evolution of Risk Management Plans in global pharmacovigilance, discuss current regulatory frameworks and components of RMPs, highlight major challenges in their implementation, and explore future perspectives for improving risk management strategies in the era of digital pharmacovigilance and real-world evidence.

Evolution of Risk Management Plans in Global Pharmacovigilance

The concept of structured risk management in pharmacovigilance has evolved

significantly over the past two decades in response to increasing concerns regarding drug safety and the limitations of traditional adverse event reporting systems. Early pharmacovigilance systems primarily relied on spontaneous reporting of adverse drug reactions (ADRs) through national and international monitoring programs. Although these systems were instrumental in identifying serious drug safety issues, they were largely reactive and often detected safety signals only after widespread exposure of patients to potentially harmful medicines (12).

Several high-profile drug safety incidents highlighted the need for more proactive approaches to drug safety monitoring. One notable example was the withdrawal of rofecoxib (Vioxx) due to increased cardiovascular risks, which emphasized the limitations of pre-marketing clinical trials in detecting rare but serious adverse events. Such events prompted regulatory agencies worldwide to strengthen pharmacovigilance frameworks and implement structured risk management strategies throughout the lifecycle of medicinal products (13).

In response to these challenges, regulatory authorities introduced formal mechanisms for proactive risk management. The International Council for Harmonisation (ICH) issued the **E2E Pharmacovigilance Planning guideline**, which established a framework for identifying potential risks and planning pharmacovigilance activities during drug development and post-marketing stages. This guideline laid the foundation for modern risk management planning by encouraging pharmaceutical companies to systematically evaluate safety concerns and implement targeted monitoring strategies (14).

The European Union was among the first regions to formally integrate Risk Management Plans into regulatory requirements. In 2005, the European Medicines Agency (EMA) introduced the **EU-Risk Management Plan (EU-RMP)** as part of its pharmacovigilance legislation. Under this framework, pharmaceutical companies are required to submit an RMP at the time of marketing authorization application and update it throughout the product lifecycle. The EU-RMP outlines known and potential safety concerns, pharmacovigilance activities designed to monitor these risks, and measures intended to minimize them (15).

Similarly, the United States Food and Drug Administration (FDA) implemented the **Risk Evaluation and Mitigation Strategies (REMS)** program under the Food and Drug Administration Amendments Act of 2007. REMS programs are designed to ensure that the benefits of certain medications outweigh their risks by requiring specific risk minimization measures such as medication guides, communication plans, restricted distribution systems, and healthcare provider training programs (16).

Over time, risk management strategies have expanded beyond traditional pharmacovigilance approaches to include more comprehensive and proactive monitoring systems. Advances in healthcare data systems have enabled the integration of real-world evidence from electronic health records, patient registries, insurance claims databases, and other large healthcare datasets. These data sources allow regulatory agencies and pharmaceutical companies to identify safety signals earlier and evaluate the effectiveness of risk minimization strategies more effectively (17).

In addition, global regulatory collaboration has played a key role in the evolution of Risk Management Plans. Organizations such as the World Health Organization (WHO), the International Council for Harmonisation (ICH), and regional regulatory networks have contributed to the development of harmonized pharmacovigilance standards and guidelines. These initiatives aim to improve international coordination in drug safety monitoring and facilitate the sharing of safety information across different regulatory jurisdictions (18).

Despite these advancements, the implementation of global risk management strategies remains complex. Differences in regulatory requirements across regions, variations in healthcare infrastructure, and challenges related to data sharing continue to pose difficulties for pharmaceutical companies operating in multiple markets. As pharmacovigilance systems continue to evolve, ongoing efforts are needed to harmonize regulatory expectations and develop innovative tools that enhance the

effectiveness of risk management strategies in ensuring patient safety (19).

Regulatory Frameworks for Risk Management Plans

Risk Management Plans (RMPs) are integral components of pharmacovigilance systems and are regulated by various international and national regulatory authorities. Different regions have established specific frameworks to ensure that medicinal products are monitored for safety throughout their lifecycle. Although the fundamental objectives of these frameworks are similar, there are notable differences in their structure, implementation, and regulatory expectations across regions.

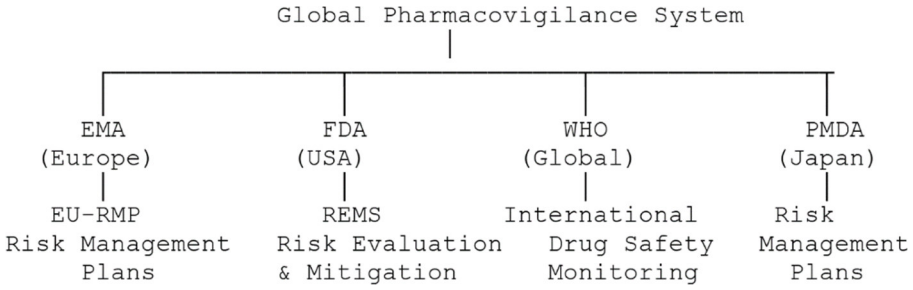

Fig 1: Global Regulatory Framework for Risk Management

European Medicines Agency (EMA)

The European Medicines Agency (EMA) has established one of the most comprehensive regulatory frameworks for Risk Management Plans through its **Good Pharmacovigilance Practices (GVP)** guidelines, particularly **Module V**, which focuses on risk management systems. In the European Union, an RMP must be submitted as part of the marketing authorization application for most new medicinal products. The EU-RMP outlines the safety profile of the product, identifies known and potential risks, and describes pharmacovigilance activities and risk minimization measures designed to monitor and manage these risks (20).

The EU-RMP includes three major components: the **safety specification**, the **pharmacovigilance plan**, and **risk minimization measures**. The safety specification summarizes important identified risks, potential risks, and missing information. The pharmacovigilance plan outlines activities such as post-authori-zation safety studies (PASS) and enhanced monitoring programs. Risk minimization measures may include routine activities such as product labeling as well as additional strategies such as educational materials and controlled access programs (21).

United States Food and Drug Administration (FDA)

In the United States, the FDA imple-ments risk management strategies through the **Risk Evaluation and Mitigation Strategies (REMS)** program. REMS are required for certain medications with serious safety concerns to ensure that their benefits outweigh potential risks. The REMS framework was introduced under the **Food and Drug Administration Amendments Act (FDAAA) of 2007** and may include elements such as medication guides, communication plans for healthcare professionals, and elements to assure safe use (ETASU), including restricted distribution systems and prescriber training requirements (22).

Unlike the EU-RMP system, REMS programs are typically required only for drugs that present significant safety concerns. The FDA regularly evaluates the effectiveness of REMS programs and may modify or discontinue them based on emerging safety data and post-marketing evidence (23).

World Health Organization (WHO)

The World Health Organization (WHO) plays a key role in promoting global pharma-covigilance practices through international collaboration and capacity-building initiatives. The **WHO Programme for International Drug Monitoring**, coordinated by the Uppsala Monitoring Centre, facilitates the collection and analysis of adverse drug reaction reports from member countries. Although the WHO does not mandate specific RMP requirements, it provides guidelines and recommendations for streng-thening national pharmacovigilance systems and

encourages the adoption of risk management strategies in drug safety monitoring (24).

Other International Regulatory Authorities

Several other regulatory agencies have implemented pharmacovigilance frameworks that incorporate risk management strategies similar to those of the EMA and FDA. For example, the **Pharmaceuticals and Medical Devices Agency (PMDA) in Japan** requires post-marketing risk management plans that include safety monitoring and risk minimization activities. Similarly, regulatory authorities such as the **Therapeutic Goods Administration (TGA) in Australia** and **Health Canada** have adopted risk management requirements aligned with international pharmacovigilance standards (25).

The increasing globalization of pharmaceutical development has highlighted the need for greater regulatory harmonization in pharmacovigilance practices. While many regulatory agencies follow similar principles based on ICH guidelines, differences in documentation requirements, timelines, and reporting standards can create challenges for pharmaceutical companies operating across multiple jurisdictions. Strengthening international collaboration and regulatory convergence remains an important priority for improving the effectiveness of global risk management strategies.

Components of Risk Management Plans

Risk Management Plans (RMPs) are structured documents designed to ensure that the benefits of a medicinal product outweigh its potential risks throughout its lifecycle. Regulatory authorities such as the European Medicines Agency (EMA) and the International Council for Harmonisation (ICH) have defined the key elements of an RMP to facilitate systematic identification, evaluation, and management of safety concerns associated with pharmaceutical products. Generally, an RMP consists of three major components: **safety specification**, **pharmacovigilance plan**, and **risk minimization measures** (26).

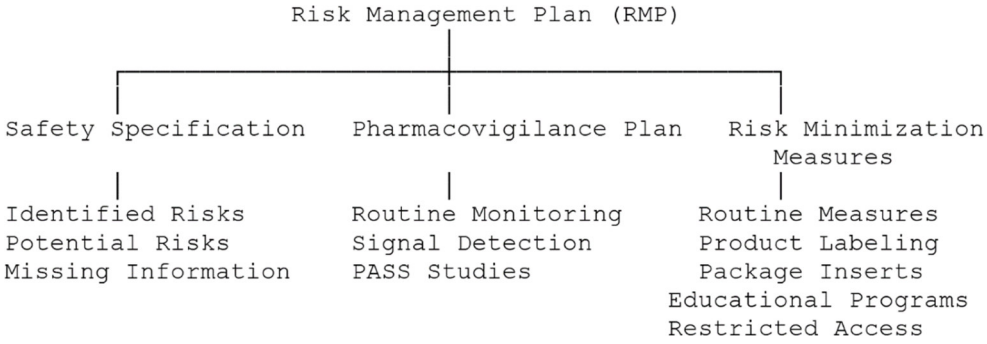

Fig 2: Structure of a Risk Management Plan (RMP)

Safety Specification

The safety specification forms the foundation of a Risk Management Plan and provides a comprehensive summary of the safety profile of a medicinal product. It includes information regarding **important identified risks, important potential risks, and missing information** related to the drug. Important identified risks refer to adverse events that have already been observed and established as being associated with the drug. Important potential risks are safety concerns that have not yet been confirmed but are suspected based on preclinical studies, clinical trials, or class effects. Missing information refers to gaps in safety data, such as lack of evidence in specific populations including pregnant women, elderly patients, or individuals with comorbid conditions (27).

The safety specification also includes epidemiological data describing the disease being treated, patient populations likely to use the medication, and potential interactions with other drugs. By summarizing known and potential risks, the safety specification helps regulatory authorities and pharmaceutical companies identify areas requiring further monitoring and risk management activities (28).

Pharmacovigilance Plan

The pharmacovigilance plan describes the activities designed to monitor, detect, and further characterize safety concerns associated

with the medicinal product. Routine pharmacovigilance activities include spontaneous adverse event reporting systems, periodic safety update reports (PSURs), and signal detection analyses conducted using pharmacovigilance databases. These activities allow regulators and manufacturers to continuously monitor the safety profile of a product once it is available in the market (29).

In addition to routine pharmacovigilance activities, additional pharmacovigilance measures may be implemented when important safety concerns require further investigation. These activities may include **post-authorization safety studies (PASS)**, observational studies, patient registries, and targeted safety monitoring programs. Such studies provide valuable real-world evidence that helps better characterize risks and evaluate their frequency, severity, and clinical impact (30).

Risk Minimization Measures

Risk minimization measures are strategies designed to prevent or reduce the occurrence or severity of adverse drug reactions associated with a medicinal product. These measures are typically classified as **routine risk minimization measures** and **additional risk minimization measures**.

Routine risk minimization measures include product labeling, package inserts, contraindications, and warnings that provide healthcare professionals and patients with information on the safe and appropriate use of the medication. These measures are considered standard regulatory requirements for most pharmaceutical products (31).

Additional risk minimization measures may be required for drugs with significant safety concerns. These measures may include educational programs for healthcare professionals, patient information leaflets, controlled distribution systems, pregnancy prevention programs, and monitoring requirements. In certain cases, regulatory authorities may require restricted access programs or specialized training for healthcare providers to ensure safe use of the medication (32).

The effectiveness of risk minimization strategies must be continuously evaluated to ensure that they successfully reduce safety risks without limiting patient access to beneficial therapies. Regulatory agencies often require periodic assessment of risk minimization measures to determine whether modifications or additional interventions are necessary. Continuous evaluation and improvement of these strategies are essential for maintaining an effective pharmacovigilance system (33).

Challenges in Global Implementation of Risk Management Plans

Despite the significant progress in pharmacovigilance systems and the widespread adoption of Risk Management Plans (RMPs), several challenges remain in their global implementation. The increasing globalization of pharmaceutical development and regulatory oversight has made risk management activities more complex. Pharmaceutical companies often need to comply with different regulatory requirements across multiple regions, which can create difficulties in maintaining consistent pharmacovigilance strategies while ensuring compliance with local regulations (34).

One of the major challenges in global risk management is the **variation in regulatory frameworks across different countries**. While organizations such as the European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), and the International Council for Harmonisation (ICH) have established structured guidelines for pharmacovigilance and risk management, differences in documentation requirements, reporting timelines, and risk minimization measures still exist. These regulatory variations can create additional administrative burdens for pharmaceutical companies and may delay the implementation of effective risk management strategies (35).

Another important challenge is the **limited availability and integration of real-world safety data**. Pharmacovigilance systems rely heavily on spontaneous adverse drug reaction reporting, which often suffers from underreporting, incomplete data, and reporting bias. As a result, important safety signals may not be detected in a timely manner. Although the increasing use of electronic health records, patient registries, and healthcare databases has improved the availability of real-world evidence, integrating and analyzing these diverse data sources remains technically challenging (36).

The **evaluation of the effectiveness of risk minimization measures** also presents a significant challenge. While regulatory authorities often require pharmaceutical companies to implement educational programs, medication guides, or restricted distribution systems to minimize risks, measuring the actual impact of these interventions can be difficult. In many cases, it is challenging to determine whether improvements in drug safety outcomes are directly attributable to specific risk minimization strategies or to other external factors such as changes in clinical practice (37).

Additionally, **resource limitations in pharmacovigilance systems** can affect the implementation of effective risk management strategies, particularly in low- and middle-income countries. Many developing countries lack well-established pharmacovigilance infrastructure, trained personnel, and comprehensive adverse event reporting systems. This can lead to gaps in safety monitoring and limit the ability of regulatory authorities to effectively evaluate and manage drug-related risks (38).

Another emerging challenge is the **management of large volumes of safety data generated by modern healthcare systems**. With the rapid growth of digital health technologies, electronic medical records, and social media platforms, pharmacovigilance systems are increasingly confronted with massive datasets that require advanced analytical tools for effective signal detection. Traditional pharmacovigilance methods may not be sufficient to handle such large datasets, highlighting the need for advanced data analytics, artificial intelligence, and machine learning approaches in drug safety monitoring (39).

Furthermore, **communication of safety information to healthcare professionals and patients** remains a critical challenge. Even when risk minimization measures are implemented, ensuring that healthcare providers and patients fully understand safety warnings, contraindications, and appropriate drug usage can be difficult. Ineffective communication strategies may reduce the effectiveness of risk management interventions and increase the likelihood of medication errors or inappropriate drug use (40).

Addressing these challenges requires stronger international collaboration among regulatory authorities, pharmaceutical companies, healthcare professionals, and academic institutions. Improving global regulatory harmonization, strengthening pharmacovigilance infrastructure, and integrating advanced data analytics technologies can significantly enhance the effectiveness of Risk Management Plans and contribute to safer use of medicines worldwide.

Future Perspectives in Risk Management and Pharmacovigilance

As pharmacovigilance systems continue to evolve, the future of Risk Management Plans (RMPs) is expected to be shaped by advancements in digital health technologies, real-world data analytics, and global regulatory collaboration. The rapid expansion of healthcare data sources, including electronic health records, insurance claims databases, patient registries, and wearable health technologies, provides new opportunities for more effective monitoring of drug safety. These data sources enable regulators and pharmaceutical companies to detect potential safety signals earlier and to evaluate the effectiveness of risk minimization strategies in real-world clinical settings (41).

One of the most promising developments in pharmacovigilance is the increasing use of **artificial intelligence (AI) and machine learning techniques** for signal detection and safety monitoring. Traditional pharmacovigilance systems rely heavily on manual review of adverse event reports, which can be time-consuming and may delay the identification of safety signals. AI-driven algorithms can analyze large volumes of safety data from multiple sources and identify patterns that may indicate emerging safety concerns. These technologies have the potential to significantly improve the speed and accuracy of signal detection and enhance the overall effectiveness of pharmacovigilance activities (42).

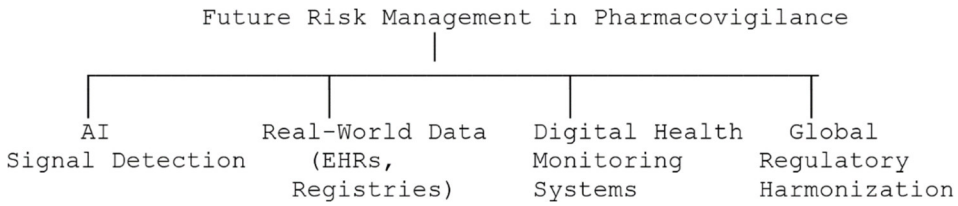

Fig 3: Future Pharmacovigilance and Risk Management Model

Another important future direction is the growing emphasis on **real-world evidence (RWE)** in risk management strategies. Real-world data obtained from routine clinical practice can provide valuable insights into drug safety across diverse patient populations, including groups that may not be adequately represented in clinical trials, such as elderly patients, pregnant women, and individuals with multiple comorbidities. Incorporating real-world evidence into Risk Management Plans allows regulatory authorities to better understand the long-term safety profile of medicinal products and make more informed regulatory decisions (43).

In addition, increasing attention is being given to the concept of **patient-centered pharmacovigilance**. Modern pharmacovigilance systems are moving toward greater involvement of patients in reporting adverse drug reactions and participating in safety monitoring programs. Patient-reported outcomes and direct patient reporting systems can provide valuable information about drug safety and treatment experiences that may not be captured through traditional healthcare reporting channels. Enhancing patient engagement can improve the quality and completeness of pharmacovigilance data and contribute to more effective risk management strategies (44).

Global regulatory harmonization is another important area of focus for the future of risk management. As pharmaceutical companies increasingly conduct multinational clinical trials and market products across multiple regions, harmonizing regulatory requirements for Risk Management Plans can help reduce duplication of efforts and improve efficiency in pharmacovigilance activities. International initiatives led by organizations such as the International Council for Harmonisation (ICH) and the World Health Organization (WHO) are working toward greater alignment of pharmacovigilance standards and risk management practices across regulatory jurisdictions (45).

Furthermore, advances in **digital pharmacovigilance and social media monitoring** are creating new opportunities for early detection of adverse drug reactions. Analysis of patient discussions on online health forums, social media platforms, and digital health applications may provide additional signals of potential drug safety issues. While these emerging data sources require careful validation and ethical oversight, they may complement traditional pharmacovigilance systems and enhance global drug safety monitoring (46).

Overall, the future of Risk Management Plans will likely involve greater integration of advanced data analytics, real-world evidence, patient engagement, and international regulatory collaboration. These innovations have the potential to strengthen pharmacovigilance systems and improve the ability of healthcare systems to ensure the safe and effective use of medicines worldwide.

Conclusion

Risk Management Plans (RMPs) have become essential components of modern pharmacovigilance systems, providing structured approaches for identifying, evaluating, and minimizing risks associated with medicinal products throughout their lifecycle. Over the past two decades, regulatory agencies worldwide have strengthened pharmacovigilance frameworks by introducing comprehensive risk management requirements, such as the European Union Risk Management Plan (EU-RMP) and the United States Risk Evaluation and Mitigation Strategies (REMS) program.

Despite these advancements, several challenges remain in the global implementation of risk management strategies. Variations in regulatory requirements, limitations in data integration, underreporting of adverse drug

reactions, and resource constraints in pharmacovigilance systems can hinder the effectiveness of risk management programs. Addressing these challenges requires improved international collaboration, stronger pharmacovigilance infrastructure, and more efficient methods for analyzing and interpreting safety data.

Emerging technologies such as artificial intelligence, big data analytics, and real-world evidence are expected to play an increasingly important role in the future of pharmacovigilance. In addition, greater involvement of patients in safety monitoring and enhanced global regulatory harmonization may further strengthen risk management practices.

In conclusion, the continuous evolution of Risk Management Plans, supported by technological innovation and global regulatory cooperation, will be crucial for improving drug safety monitoring and ensuring that the benefits of medicinal products continue to outweigh their risks in real-world clinical practice.

References

1. World Health Organization. The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: WHO; 2002.
2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255–1259.
3. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk Management Systems. EMA; 2017.
4. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategies (REMS): FDA guidance for industry. FDA; 2019.
5. Waller P, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiology and Drug Safety. 2003;12(1):17–29.
6. Council for International Organizations of Medical Sciences (CIOMS). Development and rational use of risk management plans. CIOMS; 2014.
7. Bate A, Edwards IR. Data mining techniques in pharmacovigilance. Drug Safety. 2006;29(10):939–948.
8. International Council for Harmonisation. ICH Guideline E2E: Pharmacovigilance Planning. ICH; 2004.
9. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms. Clinical Pharmacology & Therapeutics. 2013;93(6):539–546.
10. Coloma PM, Trifirò G, Patadia V, Sturkenboom M. Postmarketing safety surveillance. Drug Safety. 2013;36(3):183–197.
11. Giezen TJ, Mantel-Teeuwisse AK, Leufkens HG. Pharmacovigilance of biopharmaceuticals. Drug Safety. 2009;32(10):811–817.
12. Meyboom RH, Egberts AC, Gribnau FW, Hekster YA. Pharmacovigilance in perspective. Drug Safety. 1999;21(6):429–447.
13. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with COX-2 selective and non-selective NSAIDs. Lancet. 2005;365(9458):475–481.
14. International Council for Harmonisation. ICH Guideline E2E: Pharmacovigilance Planning. ICH; 2004.
15. European Medicines Agency. Guideline on Risk Management Systems for Medicinal Products for Human Use. EMA; 2005.
16. U.S. Food and Drug Administration. Food and Drug Administration Amendments Act (FDAAA): Risk Evaluation and Mitigation Strategies. FDA; 2007.
17. Schneeweiss S. Learning from big health care data. New England Journal of Medicine. 2014;370(23):2161–2163.
18. World Health Organization. WHO Pharmacovigilance Indicators: A Practical Manual for the Assessment of Pharmacovigilance Systems. WHO; 2015.
19. Wisniewski AF, Bate A, Bousquet C, et al. Good signal detection practices. Drug Safety. 2016;39(6):469–490.
20. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk Management Systems. EMA; 2017.
21. European Medicines Agency. Risk Management Plan Template and Guidance. EMA; 2019.

22. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategies (REMS): Guidance for Industry. FDA; 2019.
23. U.S. Food and Drug Administration. REMS Assessment Reports and Evaluation Framework. FDA; 2020.
24. World Health Organization. WHO Programme for International Drug Monitoring. Geneva: WHO; 2018.
25. Health Canada. Guidance on Risk Management Plans and Pharmacovigilance Planning. Health Canada; 2015.
26. European Medicines Agency. Risk Management Systems for Medicinal Products for Human Use. EMA; 2017.
27. International Council for Harmonisation. ICH Guideline E2E: Pharmacovigilance Planning. ICH; 2004.
28. Council for International Organizations of Medical Sciences (CIOMS). Practical Approaches to Risk Minimisation for Medicinal Products. CIOMS; 2014.
29. Edwards IR, Lindquist M. Signal detection and evaluation in pharmacovigilance. Drug Safety. 2007;30(8):607–615.
30. Schneeweiss S. Post-authorization safety studies: methodological challenges. Pharmacoepidemiology and Drug Safety. 2010;19(11):1137–1144.
31. European Medicines Agency. Guideline on Risk Minimisation Measures. EMA; 2014.
32. U.S. Food and Drug Administration. REMS Elements to Assure Safe Use (ETASU). FDA; 2018.
33. Giezen TJ, Mantel-Teeuwisse AK, Leufkens HG. Risk management of medicinal products. Drug Safety. 2009;32(5):355–364.
34. Wise L, Parkinson J, Raine J, Breckenridge A. New approaches to drug safety. Nature Reviews Drug Discovery. 2009;8(10):779–782.
35. Wiktorowicz ME, Lexchin J, Moscou K, Silversides A, Eggertson L. Keeping an eye on the pharmaceutical industry. Health Policy. 2012;108(2):95–103.
36. Trifirò G, Coloma PM, Rijnbeek PR, et al. Combining multiple healthcare databases for postmarketing drug safety surveillance. Drug Safety. 2014;37(3):143–149.
37. Banerjee AK, Zomerdijk IM, Wooder S, Ingate S, Mayall SJ. Post-authorization safety studies and risk management plans. Drug Safety. 2014;37(3):197–204.
38. Olsson S. Pharmacovigilance training in developing countries. Drug Safety. 1998;19(3):177–182.
39. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Drug Safety. 2009;32(11):1101–1114.
40. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions. Drug Safety. 2009;32(1):19–31.
41. Schneeweiss S. Learning from big health care data. New England Journal of Medicine. 2014;370(23):2161–2163.
42. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms. Clinical Pharmacology & Therapeutics. 2013;93(6):539–546.
43. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence: what is it and what can it tell us? New England Journal of Medicine. 2016;375(23):2293–2297.
44. Inácio P, Cavaco A, Airaksinen M. The value of patient reporting in pharmacovigilance. Drug Safety. 2017;40(9):737–747.
45. International Council for Harmonisation. ICH Harmonised Guideline for Pharmacovigilance Planning. ICH; 2017.
46. Sarker A, Ginn R, Nikfarjam A, et al. Utilizing social media data for pharmacovigilance. Journal of Biomedical Informatics. 2015;54:202–212.