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Regulatory Aspects of Pharmacovigilance: Global Perspectives and Challenges

Shrinivas Teli

MSc Biotechnology, Student, ClinoSol Research Pvt. Ltd.

Abstract: ***This review explores pharmacovigilance and its regulatory aspects with the current global perspective and challenges. Regulations of pharmacovigilance are created for the safety and efficacy of the available drug for the consumers. Different regulatory aspects are used during the drug's life. With the increasing complexity of medicines, there is a need for harmonization of pharmacovigilance activities across the globe. Pharmacovigilance is a global effort with regulatory agencies working together to ensure drug safety and efficacy. Globalization of pharmaceutical learnings will able to helpwith risk management factors for adverse drug reactions. Pharmacovigilance is still evolving field from the last few decades so there is some discordance between countries for these practices. Creating global harmony towards pharmacovigilance practices will lead to the safer and better use of medicines.***

Keywords: Pharmacovigilance, Regulatory aspect, Global perspective, harmonization, Clinical Research, Healthcare

1. Introduction

The word "pharmacovigilance" in which Pharmakon is the Greek word that means medicinal substance and Vigilia is a Latin word that means to keep watch. Pharmacovigilance is the science that observes the effect of medicines and prevents adverse effects on patients. It plays an important role in keeping good public health and drug regulations. Pharmacovigilance includes collecting, analyzing, and evaluating data from various sources such as clinical trials, spontaneous reports, literature, registries, and social media to detect signals of potential safety issues with medicines. These signals are then assessed for their causality, frequency, and severity to prevent side effects of the drug. [1]

Roles of pharmacovigilance

- Identification, evaluation, and prevention of adverse drug reactions (ADRs) which can range from mild to life - threatening.
- Pharmacovigilance helps detect and report ADRs, eventually improving patients' safety and efficacy.
- By maintaining the safety of a drug pharmacovigilance helps to ensure public trust for pharmaceutical industries.
- Regulatory agencies US Food and Drug Administration FDA and European Medicines Agency EMA monitor the safety of the drug and report any adverse event.
- PV is a continuous process involving the drug's safety and efficacy. Continuous monitoring can help in observing potential risks and side effects of drugs even after coming onto the market.

The first need for drug safety comes into the picture after the thalidomide disaster in 1961. In 1957thalidomide comes into the market for consumers in Europe, Asia, Australia, and America. In 1961 mothers who consumed thalidomide during pregnancy had led severe birth defects in newborn children. Around 10, 000 children got birth defects with abnormal limbs and vital organs. Right after this tragedy thalidomide is banned in many countries. [2]

This tragedy made to think about putting regulations on new medicines coming into the market. In the beginning adverse drug, reactions were collected and reported by British Yellow Card System and Food and Drug Administrations. The safety of the new drug is studied and tracked from earlier stages of development of the drug then while in the market and after reaching consumers. Adverse drug reactions of the drug and their entire life cycle are studied and reported to identify rare adverse effects.

The Council for International Organization of Medical Sciences (CIOMS) and the International Council on Harmonization (ICH) give new directions on pharmacovigilance through the risk management system. This provided to observe known and unknown risks and plan to overcome them. Now PV is becoming an emerging practice to study safety data, analyze it and communicate to reduce the potential risks. [3 - 13]

2. Comparison of the Pharmacovigilance Regulations

The evolution of PV over the past few years has seen a very big shift from a preliminary approach to a more proactive approach to risk mitigation strategies. Countries like the UK, USA, Canada, and India show discordance among PV rules and regulations. Regarding adverse effect reporting there are some major gaps found in data collection and reporting systems by different countries' regulation policies. [14 - 23]

Risk management is also an apparent factor for discordance although, in good clinical practice, recommendations are involved in different sections of the regional legislation. These aspects are not the same in the four regions, and they are never presented in the same way. Table 1 represents comparative factors of PV regulations Across four countries. [4 - 14]

Table 1: Comparison of pharmacovigilance regulations of different countries [14]

Parameter	United States	United Kingdom	India	Canada
Regulatory authority	FDA CDER CBER	MHRA CHM	CDSCO NCC PvPI IPC	Health Canada Marketed health products and food branch
Process for reporting	Through the MedWatch form and online through FAERS	Through yellow card form or via email	Paper ADR reporting form, Mobile app, via email	Online, email, Fax Telephone through Canada vigilance regional office
Pharmacovigilance system master file	Not mentioned	Maintained by the EU for each member country	Not mentioned	Not mentioned
Pharmacovigilance inspection	Via PADE inspections	Via risk assessment strategy	Not mentioned	GVP inspection program inspection strategy for GVP for drugs (POL - 0041)
Pharmacovigilance audit	Via post - approval audit inspection	In accordance with EU GVP guidelines	Not mentioned	In accordance with the GVP guidelines (gui - 0102)
Risk Management system	Given in risk management guidelines under the guidance of GVP and Pharmacoepidemiologic assessment	Follows risk management plan as EMA	As mentioned in spontaneous adverse drug reaction reporting	As mentioned in risk management plans
Serious ADR reporting time	Under 15 calendar days of the occurrence	Under 15 calendar days of the occurrence	Within 24 hours days of the occurrence	Under 15 calendar days of the occurrence
PSUR submission	TO CDER for drug products and CBER for biological products	TO PSUR repository	To DCG (1) and PvPI	Therapeutic products directorate Health Canada
Data lock point for PSUR	70/80 days	6 months	30 days	70/90 days
Safety communication	Solicited communication via the FDA website	MHRA website	CDSCO and PvPI press release	Health Canada website

FDA=Food and Drug Administration, ADR=Adverse drug reactions, EU=European Union GVP=Good pharmacovigilance practices, QPPV=Qualified Personnel for Pharmacovigilance, PADE=Post Marketing Adverse Drug Experience, UMC=Uppsala Monitoring Centre, WHO=World Health Organization, FAERS=FDA Adverse Event Reporting System, PvPI=Pharmacovigilance Programme of India, IPC=Indian Pharmacopoeia. Commission, NCC=National Coordination Centre, DCG=Drugs Controller General, CDER=Centre for Drug Evaluation and Research, CBER=Centre for Biologics Evaluation and Research, PSUR= Periodic safety update report, MHRA=Medicines and healthcare products regulatory agency, ICSRs=Individual case safety report, CDSCO=Central drugs standard control organization, CHM=Commission on human medicines, EMA=European medicines agency. [14]

3. Global Challenges Related to Pharmacovigilance Regulations

From the beginning, FDA has set standards for clinical studies. For many years FDA is very consistent in making new rules and policies for approval of the drug. Many countries have different requirements for conducting clinical trials. For globalizing research, United States scientists should come together with European Community and Canadian, Japanese, and Indian research institutions. Eastern Europe, Asia, and Latin America have a role in the advancement of regulations. The Pacific Rim was one of the fast – growing markets in pharmaceutical industries. IN 1998 EC and Japan's Good Clinical Practice regulations were more advanced than top US regulations. World Health Organisation presented GCP which was like EC guidelines. Combining efforts for marketing approval is the final goal of globalization in drug research. The US was not approving other countries' regulatory bodies' decisions. Making international efforts by EC, Japan and the US can make a significant role in harmonizing clinical practices. [17]

Medicines and Healthcare Products Regulatory Agency (MHRA) is an agency that controls the safety and efficacy of medicines and medical devices in the UK. The Pharmacovigilance Programme of India (PvPI) is an organization in India's response to drug problems. It plays the role of receiving all adverse events of medicines and taking actions related to them.

(FDA) Food and Drug Administration is established in 1906 for the safety and efficacy of the drugs. This authority is increased in 1938 to regulate drugs and in 1976 for devices. Regulatory requirements vary according to product types and risk follows with it. One other route to market is through the premarket notification for which devices are evaluated as their equivalence to devise marketed prior to May28, 1976. [16 - 22] Many times, manufacturers need to provide clinical data in investigational device exemption format for equivalence. Investigational new drug Application (IND) approves new drug products for clinical trials. FDA is constantly evolving making changes in its guidelines to improve PV. [16]

Need for Proactiveness among all stakeholders in PV including health authorities, pharmaceutical industries, healthcare professionals, and consumers. Whatever work is

happening related to PV is according to the existing PV legislation. Making significant and defining changes in PV legislation will also lead to changes in the use of medicines in safer and more effective ways. There are many differences in adverse drug reaction reporting and risk management policies across countries. When drug safety reporting is different for each regulatory authority then maintaining risk management becomes a difficult task and making new rules and regulations for the safety of medicines will not be possible. For example, in 1997 and 2005 US and EU withdraw 22 drugs from the market because of the discoordination of risk management requirements between them. [3]

4. International Efforts in Harmonisation of Pharmacovigilance

ICH, CIOMS, and WHO efforts taken by these organizations made significant changes in the regulations of PV practices. Still risk management systems and adverse event reporting systems still have not been addressed yet. [3] Reporting requirements are varying among different regulatory authorities If different data on thesame product is submitted by manufacturers and healthcare professionals to regulatory authorities, then there is a lack of communication. This also leads to variation and delays in addressing major public health issues. [4 - 10]

Understanding safety issues and agreeing on a common safety reporting system and avoiding miscommunication will strengthen the worldwide PV system. The three most important global groups are World Health Organisation, the ICH technical aspect in pharmaceutical, CIOM, and their strategies towards building safer medicines. Increasing PV education in colleges, universities, and trainers will able to reduce unawareness of PV. For real transformation, we need to address disharmony, miscommunication, and discoordination. Then this practice will be harmonized internationally and also by agreeing on the best communication technologies available for advancement. [4 - 5]

Some of the global authorities have clearly failed to adopt international guidelines ICH and policies completely. There is a system available where safety data is shared in different areas wherever there are medicines. [6 - 7] We should take the help of technology for better communication between regulatory agencies, pharmaceutical industries, healthcare professionals, and consumers. It is possible to establish an alert system in PV practices by Google. By using Cloud computing we should store subject files available and unchanged. Making PV truly computerized will help to reduce biases increasing the capacity and avoiding clinically irrelevant data. [9 - 14]

All PV professionals must be aware ofthe latest trends and technological advancements. By making use of these technologies, we can overcome the disharmony in pharmacovigilance practices and improve the harmony towards it. [10 - 12]

5. Future Directions

The future directions of regulatory aspects of pharmacovigilance are likely to focus on several areas, including:

Greater use of real - world data: There is an increasing emphasis on using real - world data (RWD) to support pharmacovigilance activities. The use of RWD can provide more accurate and timely information on drug safety and efficacy, as well as enable more effective risk management strategies.

Digitalization and automation: The pharmaceutical industry is moving towards greater digitalization and automation, which is expected to improve the efficiency and accuracy of pharmacovigilance processes. This includes the use of artificial intelligence (AI) and machine learning (ML) algorithms to analyze large datasets, identify potential safety issues, and prioritize signals for further investigation.

Improved global collaboration: As the pharmaceutical industry becomes increasingly globalized, there is a need for greater collaboration between regulatory authorities and other stakeholders in different countries. This will enable better sharing of information and resources, and help to harmonize pharmacovigilance standards and practices across different regions.

Patient involvement: There is a growing recognition of the importance of involving patients in pharmacovigilance activities. Patients can provide valuable insights into the real - world use of drugs, and their experiences and perspectives can help to identify safety issues and inform risk management strategies.

Proactive risk management: Finally, there is a trend towards more proactive risk management strategies, which focus on identifying and mitigating potential safety issues before they become significant problems. This includes the use of predictive analytics and other advanced tools to identify emerging safety signals and develop targeted risk management strategies.

6. Conclusion

Pharmacovigilance is a global effort with regulatory agencies working together to ensure drug safety and efficacy. Besides progress in PV, there are still issues in medicines safety. Harmonisation in PV requires a specific but influencing implementation of a ‘best suitable practice’ for healthcare people regulatory bodies, and industries. So that these professional people will unite and work together. Still, there is a need for training for PV professionals for better and more advanced communication tools and technologies. Safety information should be communicated between different regulatory agencies, manufacturers, healthcare professionals, and consumers. All these practices need the use of various tools for communicating from product labeling to adverse events reporting. All this is happening through social media but in the future, we should find out a new mode of communication should be found for best PV practices. [11]

Finding out discordance between existing practices is just a small step however there is a need for the best skills, infrastructure, communication tools, and technologies required for the future advancement of PV. All the regulatory bodies should work together and focus on increasing knowledge about PV and focusing on its safety and efficacy of it. [12]

PV requires scientific development in the right balance between good academic basics, and strong training in newer innovations in technologies that are dedicated to PV practices. Finding out the discoordination between different legislations of different countries and allowing international coordination. In this way, pharmacovigilance practices will be able to establish harmonization. [13]

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