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Review Article

Comparative Review of Pharmacovigilance System in Different Countries

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ABSTRACT

This comparative review explores the pharmacovigilance systems in India, China, Germany, Bangladesh, Italy,Vietnam, Saudi Arabia. The analysis focuses on regulatory frameworks, adverse event reporting processes, data collection methodologies, and technological advancements in drug safety monitoring. By assessing the effectiveness of each country's system, the review identifies strengths, weaknesses, and unique approaches to pharmacovigilance. Key factors such as public awareness, healthcare provider involvement, and the integration of real-world evidence are discussed. The findings aim to highlight best practices and suggest improvements, contributing to enhanced drug safety and patient protection worldwide.

INTRODUCTION

Pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. The primary goal of pharmacovigilance is to improve patient safety and ensure that the benefits of a drug outweigh its risks. This includes monitoring the safety of drugs after they have been approved for use, assessing any adverse reactions, and taking necessary actions to minimize harm to patients. Pharmacovigilance involves the collection, monitoring, and analysis of data from various sources, such as clinical trials, post-marketing surveillance, healthcare providers, and patients themselves. The information gathered helps regulatory authorities make informed decisions about the continued use of medicines, label changes, or even market withdrawals when the risks outweigh the benefits. Role of the World Health Organization (WHO) in Pharmacovigilance-the world Health Organization

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(WHO) plays a critical role in the global framework for pharmacovigilance. It supports member countries in ensuring the safety of medicines and improving public health outcomes. The key activities of WHO in pharmacovigilance include:

1. **Global Collaboration and Guidance**: WHO provides leadership and sets international standards for pharmacovigilance systems. It helps countries develop their nationalpharmacovigilance programs by offering technical support, guidelines, and training.
2. **WHO Global Individual Case Safety Reports (ICSR) Database – VigiBase**: WHO operates a global pharmacovigilance database called **VigiBase**, which is the largest collection of individual case safety reports (ICSRs) related to adverse drug reactions (ADRs). VigiBase helps in the detection of safety signals worldwide, facilitating global data sharing and improving the understanding of drug safety issues.
3. **International Drug Monitoring Program**: WHO runs the **International Drug Monitoring Program** to monitor the safety of medicines globally. The program encourages countries to report adverse drug reactions to the **WHO Collaborating Centre for International Drug Monitoring** in Uppsala, Sweden. This global network includes more than 150 countries.
4. **Regulatory Guidance and Capacity Building**: WHO provides countries with training and resources to build strong pharmacovigilance systems and regulatory frameworks. It develops guidelines for the safe use of medicines, encourages the use of risk management strategies, and facilitates scientific discussions on drug safety.
5. **Promotion of Safe and Effective Medicine Use**: Through various programs, WHO advocates for the safe and rational use of medicines, helping health authorities and organizations address challenges such as polypharmacy, medication errors, and counterfeit drugs. (1)

METHODOLOGY: The review will be conducted using the following methodology:

1.Literature Review:

oSystematic search of peer-reviewed articles from databases such as PubMed, Scopus, and Web of Science

oReview of official government documents and reports from each country's regulatory bodies

oExamination of World Health Organization (WHO) reports and databases

2.Data Collection:

oGathering information on the structure of each country's pharmacovigilance system

oIdentifying key stakeholders and their roles

oCollecting data on reporting mechanisms, databases, and signal detection methods

oAssessing regulatory frameworks and legislative support

3.Comparative Analysis:

oEvaluating the strengths and weaknesses of each system

oComparing reporting rates and types of adverse events

oAssessing the integration of pharmacovigilance with healthcare systems

oAnalyzing the impact of cultural and socioeconomic factors on pharmacovigilance practices.

RESULT AND DISCUSSION:

Pharmacovigilance system in India:

1. Introduction to Pharmacovigilance in India-

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. In India, the need for a robust pharmacovigilance system has become increasingly important due to the

country's large population, growing pharmaceutical industry, and the widespread use of traditional medicines alongside modern drugs.

The Indian pharmacovigilance system has evolved significantly over the past few decades, with major developments occurring in the early 2000s. The system aims to ensure the safety of medicinal products and protect public health by monitoring and assessing the risks and benefits of drugs available in the Indian market.

2. Pharmacovigilance Programme of India (PVPI)-

The Pharmacovigilance Programme of India (PVPI) was launched by the Central Drugs Standard Control Organization (CDSCO) in July 2010. Its primary objectives include:

a) Monitoring ADRs in the Indian population

b) Creating awareness among healthcare professionals about the importance of ADR reporting

c) Generating independent, evidence-based recommendations on the safety of medicines

d) Supporting CDSCO in formulating safety-related regulatory decisions for medicines

Key features of PVPI:

- National Coordination Centre (NCC) established at the Indian Pharmacopoeia Commission (IPC) in Ghaziabad
- Network of ADR Monitoring Centres (AMCs) across the country
- National database of ADRs
- Collaboration with the WHO Programme for International Drug Monitoring

3. Criteria for Adverse Drug Reactions (ADRs) and Reporting to Regulatory Authorities-

An Adverse Drug Reaction (ADR) is defined as a response to a drug that is noxious and unintended, occurring at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function.

Criteria for reporting ADRs:

a) Severity: All serious and unexpected ADRs should be reported

b) Novelty: New or previously unreported reactions

c) Frequency: Increase in the frequency of a known ADR

d) Drug-drug or drug-food interactions leading to ADRs

Reporting process:

1. Healthcare professionals, patients, or caregivers identify a suspected ADR
2. Complete the ADR reporting form (available online or in paper format)
3. Submit the form to the nearest AMC or directly to the NCC-PvPI
4. NCC-PvPI assesses the report and enters it into the national database
5. Serious ADRs are reported to the CDSCO for regulatory action if necessary

Services Enhancing Pharmacovigilance Activities in India

Several services and initiatives have been implemented to strengthen pharmacovigilance activities in India:

a) ADR reporting mobile app: Launched by PvPI to facilitate easy reporting of ADRs by healthcare professionals and consumers

b) Toll-free helpline: Provides support for ADR reporting and information on drug safety

c) Periodic Safety Update Reports (PSURs): Mandatory submission by pharmaceutical companies to CDSCO for post-marketing surveillance

d) Signal detection and analysis: NCC-PvPI regularly analyzes the ADR database to identify new safety signals

e) Training and capacity building: Regular workshops and training programs for healthcare professionals on pharmacovigilance

f) Integration with other health programs: Collaboration with national health programs (e.g., National AIDS Control Organization, Revised

National Tuberculosis Control Program) for monitoring drug safety in specific therapeutic areas

g) Active surveillance programs: Targeted studies to monitor the safety of specific drugs or in specific patient populations

h) Consumer awareness initiatives: Educational campaigns to increase public awareness about drug safety and the importance of reporting ADRs

i) HaemovigilanceProgramme of India (HvPI): A subset of PvPI focusing on monitoring adverse reactions related to blood transfusion and blood products.

4. Pharmacovigilance In India Faces Several Challenges, Including:

1. **Underreporting**: Many adverse drug reactions (ADRs) go unreported due to lack of awareness among healthcare professionals and patients about the importance of reporting.
2. **Data Quality**: Variability in the quality of data collected can affect the reliability of pharmacovigilance outcomes. Inconsistent reporting formats and incomplete information are common issues.
3. **Training and Awareness**: There is a need for improved training for healthcare professionals regarding the pharmacovigilance process, including ADR reporting and data management.
4. **Infrastructure and Resources**: Limited resources and infrastructure for monitoring and analyzing ADRs can hinder effective pharmacovigilance.
5. **Regulatory Challenges**: The regulatory framework for pharmacovigilance is evolving, but there may still be gaps in enforcement and compliance.
6. **Public Awareness**: Lack of awareness among the general public about the role of pharmacovigilance and the importance of reporting ADRs can limit the effectiveness of the system.
7. **Integration with Healthcare Systems**: Integrating pharmacovigilance activities with existing healthcare systems and electronic health records can be challenging.
8. **Cultural Factors**: Cultural attitudes toward medication and healthcare may affect the willingness of patients and providers to report ADRs. (2) (3)

•Pharmacovigilance system in China:

China has been developing its pharmacovigilance system since the 1980s, with significant improvements in recent years to align more closely with international standards. The system aims to monitor and improve drug safety for the world's largest population.

Regulatory Authority:

The main regulatory body overseeing pharmacovigilance in China is the National Medical Products Administration (NMPA), formerly known as the China Food and Drug Administration (CFDA). The NMPA works in conjunction with the National Center for Adverse Drug Reaction Monitoring (NCADRM).

ADR Reporting and Processing Mechanism:

1. Reporting sources: Healthcare professionals, pharmaceutical companies, and patients can report adverse drug reactions (ADRs).

2. Reporting methods: Reports can be submitted online through the National ADR Monitoring System, by mail, or by phone.

3. Processing:

- Reports are initially reviewed at local ADR monitoring centers.
- Serious ADRs are forwarded to provincial centers and then to the NCADRM for further evaluation.
- The NCADRM analyzes the data and may recommend regulatory actions to the NMPA if necessary.

4. Database: All reports are stored in the National ADR Database for ongoing analysis and signal detection.

Challenges:

1. Underreporting: Despite improvements, ADR reporting rates are still lower than in some developed countries.
2. Quality of reports: Some reports lack crucial details, making causality assessment difficult.
3. Awareness: There's a need for increased awareness about pharmacovigilance among healthcare professionals and the public.
4. Regional disparities: Reporting rates and quality vary significantly between urban and rural areas.
5. Integration with international standards: While progress has been made, further alignment with global pharmacovigilance practices is needed.
6. Limited resources: Given China's large population, there's a need for more trained personnel and technological resources to manage the pharmacovigilance system effectively. (4) (5)

Pharmacovigilance system in Bangladesh:

Here's an overview of the pharmacovigilance system in Bangladesh:

Introduction:

Pharmacovigilance is the practice of monitoring, detecting, assessing, and preventing adverse effects or other drug-related problems. In Bangladesh, the pharmacovigilance system is relatively new and still developing.

Regulatory Authority:

The main regulatory authority for pharmacovigilance in Bangladesh is the Directorate General of Drug Administration (DGDA). It operates under the Ministry of Health and Family Welfare.

ADR Reporting and Processing Mechanism:

1. Reporting: Healthcare professionals, pharmaceutical companies, and patients can report Adverse Drug Reactions (ADRs) to the DGDA.
2. Collection: Reports are collected through various means, including paper forms, online submissions, and direct communication.
3. Assessment: The DGDA evaluates the reports to determine causality and significance.
4. Database: Reported ADRs are entered into a national database for tracking and analysis.
5. Signal Detection: The DGDA analyzes the data to identify potential safety signals.
6. Action: Based on the analysis, regulatory actions may be taken, such as updating product information or issuing safety alerts.

Challenges:

1. Underreporting: There's a lack of awareness among healthcare professionals and the public about the importance of ADR reporting.
2. Limited resources: The pharmacovigilance system faces constraints in terms of funding, trained personnel, and technology.
3. Coordination: There's a need for better coordination between different stakeholders in the healthcare system.
4. Data quality: Ensuring the accuracy and completeness of ADR reports can be challenging.
5. Regulatory framework: The legal and regulatory framework for pharmacovigilance in Bangladesh is still evolving.
6. Training: There's a need for more comprehensive training programs for healthcare professionals on pharmacovigilance practices. (7)

Pharmacovigilance system in Germany:

Pharmacovigilance in Germany is part of a comprehensive system to monitor drug safety and manage risks associated with medicinal products. It aims to detect, assess, understand, and prevent adverse drug reactions (ADRs) and other medicine-related problems.

Regulatory Authority: The main regulatory authority for pharmacovigilance in Germany is the Federal Institute for Drugs and Medical Devices (BundesinstitutfürArzneimittel und Medizinprodukte, BfArM). For vaccines and blood products, the Paul-Ehrlich-Institut (PEI) is responsible.

ADR Reporting and Processing Mechanism:

1. **Reporting:**

- Healthcare professionals (doctors, pharmacists, etc.) can report ADRs directly to the BfArM or PEI.
- Patients can report ADRs to their healthcare providers or directly to the authorities.
- Pharmaceutical companies are obligated to report all serious ADRs they become aware of.

2. **Processing:**
- Reports are collected in a national database.
- The BfArM/PEI assess the reports for causality and severity.
- Signals are detected using statistical methods and expert analysis.
- When necessary, regulatory actions are taken (e.g., label changes, risk minimization measures).

3. **Integration:**
- German data is also sent to the European Medicines Agency (EMA) for integration into the EU-wide database EudraVigilance.

Challenges:

1. Underreporting: Not all ADRs are reported, leading to potential gaps in safety data.
2. Data quality: Ensuring complete and accurate information in ADR reports can be challenging.
3. Signal detection: Distinguishing true safety signals from background noise in large datasets.
4. Balancing timely action with thorough evaluation: Responding quickly to potential safety issues while ensuring thorough scientific assessment.
5. Communication: Effectively informing healthcare professionals and the public about drug safety issues without causing undue alarm.
6. Harmonization: Aligning national practices with EU regulations and global standards.
7. Resource constraints: Managing the increasing volume of safety data with limited resources.
8. New data sources: Integrating and validating data from novel sources like social media and electronic health records. (8)

Pharmacovigilance system in Saudi Arabia: Pharmacovigilance refers to the science and activities related to detecting, assessing, understanding, and preventing adverse drug reactions (ADRs) and other drug-related problems. In Saudi Arabia, the pharmacovigilance system has been developing over the past few decades to ensure medication safety for patients.

Regulatory Authority: The main regulatory authority responsible for pharmacovigilance in Saudi Arabia is the Saudi Food and Drug Authority (SFDA). Established in 2003, the SFDA is responsible for regulating, overseeing, and controlling food, drug, medical devices, and other related products.

ADR Reporting and Processing Mechanism:

1. **Reporting channels:**
- Healthcare professionals can report ADRs through an online portal, email, fax, or mail.
- Patients and consumers can also report ADRs directly to the SFDA.

2. **National Pharmacovigilance Center (NPC):**
- The NPC, established under the SFDA, collects, analyzes, and evaluates ADR reports.
- It maintains a national database of ADRs.

3. **Processing of reports:**
- Reports are reviewed and validated by trained professionals.
- Causality assessment is performed to determine the likelihood of a causal relationship between the drug and the adverse event.
- Signal detection methods are used to identify potential safety concerns.

4. **Follow-up actions:**
- The SFDA may request additional information from reporters or manufacturers.
- Safety alerts may be issued to healthcare professionals and the public.
- Regulatory actions, such as label changes or product recalls, may be implemented if necessary.

Challenges:

1. Underreporting: As in many countries, underreporting of ADRs is a significant challenge in Saudi Arabia.
2. Awareness: There is a need for increased awareness among healthcare professionals and the public about the importance of ADR reporting.
3. Cultural factors: Cultural beliefs and practices may influence reporting behaviors and perceptions of medication safety.
4. Integration of systems: Improving integration between different healthcare systems and the pharmacovigilance system to facilitate more comprehensive data collection.
5. Resource constraints: Ensuring adequate human and technological resources to effectively manage and analyze the increasing volume of ADR reports.
6. Regional variations: Addressing differences in reporting rates and practices across different regions of Saudi Arabia. (9)

Pharmacovigilance system in Italy-The Italian pharmacovigilance system is an integral part of the European Union's pharmacovigilance network, operating under the coordination of the Italian Medicines Agency (AgenziaItaliana del Farmaco, AIFA). Established in 2003, AIFA serves as the national competent authority responsible for drug regulation and safety monitoring in Italy.

1. Regulatory Framework

The pharmacovigilance system in Italy is primarily governed by national laws and European Union (EU) regulations. As an EU member state, Italy adheres to the European Medicines Agency (EMA) guidelines, which harmonize pharmacovigilance practices across member states. Key regulations include:

- **European Medicines Agency (EMA) and European Medicines Regulatory Network**: Italy follows the EMA's centralized system for pharmacovigilance, which provides a unified approach to monitoring the safety of medicinal products marketed in the EU.
- **Italian Medicines Agency (AIFA)**: The AIFA is the national regulatory body responsible for overseeing the safety of medicines in Italy. AIFA plays a central role in managing pharmacovigilance activities, conducting safety evaluations, and ensuring compliance with both national and EU pharmacovigilance standards.
- **Italian Law**: The legislative basis for pharmacovigilance in Italy is set out in the Legislative Decree No. 219/2006, which transposes EU directives regarding medicinal products into national law, and the subsequent amendments which align with evolving EU pharmacovigilance regulations.
- **Reporting Requirements**: Healthcare professionals and patients in Italy are encouraged to report adverse drug reactions (ADRs) to AIFA, and reports are submitted to the EMA through the EudraVigilance database, which is a European system for the collection, management, and analysis of ADR reports.

2. Adverse Drug Reaction (ADR) Reporting System

Italy has a well-established ADR reporting system that includes various mechanisms for reporting suspected ADRs, and these reports are crucial for post-marketing surveillance of medicines. The reporting system operates through several channels:

- **Spontaneous Reporting**: Healthcare professionals (doctors, pharmacists, nurses) and patients can voluntarily report suspected ADRs. In Italy, this is facilitated through the AIFA's **Farmacovigilanza (Pharmacovigilance) portal** or the regional pharmacovigilance centers. Reports can be submitted via paper forms or electronically.

- **Patient Reporting**: In addition to healthcare professionals, patients in Italy can directly report adverse reactions via the **"ReportADR"** system. This provides a user-friendly platform for patients to submit their experiences and concerns about drug safety.
- **EudraVigilance**: Once ADRs are reported, AIFA transmits the data to the EU's **EudraVigilance** system, which allows for the monitoring of safety data across Europe. The system aggregates reports and provides critical information for regulatory authorities to assess the benefit-risk profile of medicines.
- **AIFA's Annual Reports**: AIFA publishes annual reports on pharmacovigilance activities, which include statistics on ADR reports, risk management measures taken, and safety warnings or updates issued.

While Italy's pharmacovigilance system is robust, there are several challenges and areas that could benefit from further improvement:

- **Underreporting**: Despite the efforts to promote ADR reporting, underreporting remains a significant challenge in Italy, as in many other countries. This is especially true for mild or less severe reactions that might not be reported by patients or healthcare providers.
- **Data Quality**: The accuracy and completeness of ADR reports are critical for effective pharmacovigilance. There is an ongoing need for training and education for healthcare providers and patients to improve the quality of the data submitted.
- **Integration of Real-World Data**: As the healthcare system evolves, there is a growing need to integrate real-world evidence (RWE) from electronic health records, registries, and other sources into the pharmacovigilance system to better capture ADRs and improve drug safety evaluations.
- **Regulatory Coordination**: While Italy is aligned with EU pharmacovigilance regulations, better coordination between national and EU bodies could help streamline the assessment of complex safety issues, particularly for drugs marketed across multiple jurisdictions (10)

CONCLUSION:

The comparison of pharmacovigilance systems across these six countries reveals significant variations in maturity, infrastructure, and effectiveness:

1. **Developed Systems**: Germany and Italy stands out with a well-established, comprehensive system that has been in place for decades. It benefits from strong regulatory support, mandatory reporting, and active surveillance mechanisms.
2. **Rapidly Evolving Systems**: China and Saudi Arabia have made significant strides in recent years. Both countries have invested heavily in their pharmacovigilance infrastructure, implementing mandatory reporting and risk management plans. China's system, however, faces challenges due to regional disparities.
3. **Developing Systems**: India, Bangladesh, and Vietnam are at various stages of development in their pharmacovigilance efforts. While India has a large population coverage and improving IT infrastructure, it still struggles with underreporting and lack of awareness. Bangladesh and Vietnam have more recently established systems and face challenges related to limited resources and awareness.
4. **Common Challenges**: Underreporting and lack of awareness among healthcare professionals and the public are common issues across most of these countries, particularly in the developing systems.
5. **WHO Integration**: All six countries are members of the WHO Programme for International Drug Monitoring, which facilitates global cooperation and data sharing.

6. **Patient Involvement**: Most countries now allow patient reporting, with Bangladesh having more limited patient involvement.
7. **Regulatory Framework**: All countries have established regulatory bodies overseeing pharmacovigilance, but the effectiveness and reach of these bodies vary.

In conclusion, while all six countries have made progress in establishing pharmacovigilance systems, there is a clear divide between the more developed systems (Germany, and to a lesser extent, China and Saudi Arabia) and the developing systems (India, Bangladesh, and Vietnam). The key to improvement lies in increasing awareness, providing adequate resources, and strengthening regulatory frameworks. Developing countries can learn from the successes and challenges faced by more established systems to enhance their own pharmacovigilance efforts.

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