

Drug Safety Monitoring of Globally Withdrawn Medicines Still Available in India

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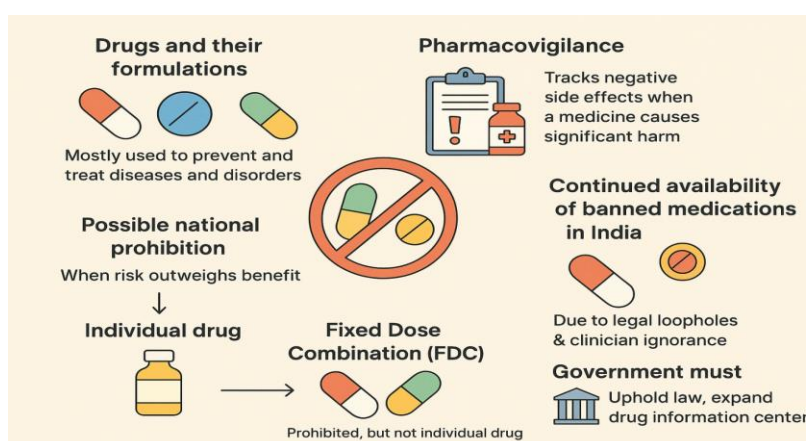
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ABSTRACT

Drugs and their formulations are mostly used to prevent and treat diseases and disorders; only a small percentage of these medications are deemed necessary and life-saving, while others continue to be stand-ins for one another. Pharmacovigilance is used to track negative side effects when a medicine's use causes significant harm to the general public; when the risk outweighs the benefit, the substance is considered for possible national prohibition. Certain medications only intensify their negative effects when taken with another drug, which is deemed unreasonable; in these cases, the Fixed Dose Combinations FDC is prohibited, but not the individual drug. The continued availability of banned medications in India may be the result of both the continued existence of legal loopholes pertaining to the clearance and production of pharmaceuticals as well as clinicians' ignorance and ignorance. The government must uphold the law, expand drug information centers, and guarantee their efficient operation so that physicians and the general public can receive the most recent information on each medication.

Keywords: ADR; adverse drug reactions; banned drugs; DCGI; governing laws; NPP; National Pharmacovigilance Program; pharmacovigilance; regulatory bodies.

Graphical Abstract globally discarded but still available in Indian market



INTRODUCTION

Given the current state of illness prevalence, ensuring the quality of medications with established therapeutic benefits and minimal negative side effects is a top priority for pharmaceutical companies, physicians, and other healthcare professionals. [1, 2, 3] The main

variables that determine whether a drug should be used or banned include unexpected negative side effects, unnecessary toxic effects, the availability of safer alternatives, harmful interactions, irrational combinations, and the possibility of management failures. When post-marketing surveillance reveals that a medicine is hazardous, developed nations promptly prohibit its manufacture and sale through regulatory agencies.

But in India, the process of banning a medication is drawn out and time-consuming, which is the main reason why pharmaceuticals that are prohibited in other nations continue to be available on the market. [2, 4] Insufficient ADR information regarding these medications has been disseminated, which is another significant factor contributing to their availability. [5]. In addition to comparing drug safety monitoring systems in developed nations and offering suggestions for enhancing an Indian system that can ensure the safety and effectiveness of drugs, the current review thoroughly examines the drugs that are prohibited in other nations but are still sold in Indian markets, as well as the reasons behind their continued availability.

Pharmacovigilance

Most nations have established pharmacovigilance centres. The international collaboration center is the Uppsala Monitoring Centre in Sweden. In order to gather adverse drug reaction (ADR) data nationwide, the Ministry of Health and Family Welfare at AIIMS, New Delhi, established the National Pharmacovigilance Program (NPP) in 2010. The NPP includes a national coordinating center that uses a VIGIFLOW software interface run by the Uppsala Monitoring Center to gather ADR data from various pharmacovigilance centres across the nation regarding the cause, problem, and personnel involved in an adverse drug event. The information produced by pharmacovigilance serves as the official drug usage guideline and is helpful in teaching medical professionals about adverse drug reactions. Because it provides the foundation for evaluating the safety and effectiveness of medications, it plays a vital role in the sensible use of pharmaceuticals. [6]

Pharmacovigilance's activities include :

- a) ADR monitoring techniques include post-marketing surveillance, electronic medical record linkage, prescription event monitoring, doctor-intentional reporting, and other cohort/case-control studies. Health care providers' creativity and readiness are key factors in voluntary reporting. While less than 10% of ADRs are voluntarily reported even in wealthy nations, it is insignificant in India. Melodramatic reactions and those that happen instantly are typically noted. This approach does not reveal the incidence of the response, even though it can detect rare reactions.
- b) disseminating information about adverse drug reactions (ADRs) through "drug alerts," "medical letters," and advisories that pharmaceutical companies and regulatory bodies (such the FDA in the USA, MPA in Sweden, NAM in Finland, etc.) send to medical practitioners.
- c) Drug usage restrictions or statutory warnings, precautions, or even the removal of the drug are indicated by changes in the categorization of drugs. [6,8]

Adverse Drug Reactions

The majority of medications have the potential to have negative side effects, and there is always a risk involved when a certain medication is administered. When deciding whether to continue or stop a specific medication in a patient, the amount of risk must be weighed against the amount of anticipated therapeutic benefit. For instance, in the case of organ transplantation, even the risk of immunosuppression from immunosuppressive drugs and

steroids may be warranted, yet minor sleepiness from antihistamines used to treat allergies and the common cold may not be acceptable. ADRs are divided into two categories: weird (type B) and augmented (type A). [9,10]

ADR Reporting

ADR management is said to be based on healthcare providers' intention to report ADRs. Typically, reporting is started verbally by letter to the relevant organisation and electronically using an internet portal. In the current environment, electronic reporting is becoming more and more common. Table1.

Country	Reporting System	Organizaton
UK	Yellow Card (Paper British National Formulary BNF).Electronic Yellow Card (CSM/ MCA website).	MCA: Licensing Division
Netherlands	Reporting from available in the Dutch equivalent of the national formulary.	Lareb(Netherlands Pharmacovigilance Foundation)
USA	Medication error reporting program MedMARx,National Nosocomial Infection Survey,Sentinel Events Reporting Program ,MedWatch	ISMP-Institute for Safe Medication Practices United States Pharmacopoeia Centre for Disease Control board FDA
Canada	CADRMP: Canadian Adverse Drug Reaction Monitoring Program	ADR reporting form through Compendium of Pharmaceuticals & Specialities (CPS)
New Zealand	CARM: Centre for adverse drug reactions monitoring,IMMP: The Intensive Medicines Monitoring Program	Electronic / online via CARM website
Sweden	MPA	Form via MPA
India	Indian pharmacopeia commission	Suspected ADR reporting form(Red form)

Regulatory Status of Drugs In India

An enormous market for illogical FDCs that combine prohibited pharmaceuticals has grown in India over the last ten years; this has been attributed to pharmaceutical corporations' relentless efforts to raise their profile among consumers and medical professionals. Because the safety, efficacy, and bioavailability of the unique active pharmaceutical ingredient may change when two or more drugs are combined, 122E of the Drug and Cosmetics Rule suggests that a combination of two or more medications be regarded as a "new drug," and that all novel combinations must be legally approved by the Drugs Controller General, India (DCGI).

The following is the practice of approval in the current situation: Although they lack this legal authority, state drug controllers (SDCs) can and do provide certificates for the approval and marketing of novel combinations. Despite not being approved by the DCGI or other SDCs, a medicine can be traded or sold in any state in the nation once it has been approved

by an SDC. The regulations that govern the marketing and accreditation of pharmaceuticals in India lack a clear definition. [3, 4]

The final authority to impose a drug ban is the Drug Technical Advisory Board (DTAB). The process of processing a ban involves designating an executing committee to investigate the drug's harmful effects. [3,4,5]

Chapter 1: Overview of Pharmacovigilance

The Evolution of Pharmacovigilance:

Pharmacovigilance, the science of monitoring the safety of medicines and identifying, assessing, and preventing adverse drug reactions (ADRs), has evolved significantly over the years. The development of pharmacovigilance is closely tied to historical events that have highlighted the need for robust drug safety systems. Below is a detailed timeline of the evolution of pharmacovigilance, from its early beginnings to its current global practices.

1. Early Beginnings: The Need for Drug Safety Awareness

Before the 1960s, there was limited attention to the long-term safety of drugs. Most medicines were introduced into the market without extensive post-marketing surveillance or monitoring systems. However, adverse drug reactions and medication-related harm were not systematically tracked or reported, which led to significant public health issues.

2. The Thalidomide Tragedy (1950s-1960s)

The thalidomide tragedy marked a pivotal moment in the history of pharmacovigilance and brought global attention to the importance of monitoring drug safety.

Thalidomide was introduced in the late 1950s as a sedative and treatment for morning sickness in pregnant women. In the early 1960s, reports of severe birth defects caused by thalidomide began to emerge, including deformities in babies born to women who had taken the drug during pregnancy.

Impact on Drug Safety:

Thalidomide's widespread use and the devastating effects it had on thousands of babies highlighted the risks of inadequate testing and post-marketing surveillance. The tragedy underscored the need for more rigorous safety monitoring of drugs, especially those used by vulnerable populations like pregnant women.

Global Response:

The thalidomide disaster led to significant changes in drug regulatory systems worldwide, especially in the United States and Europe. In 1962, the U.S. Food and Drug Administration (FDA) strengthened its drug approval process, requiring more extensive pre-market clinical trials and increased post-marketing surveillance to monitor drug safety.

3. Formation of Regulatory Bodies and Initiatives (1960s-1970s)

- **Establishment of the WHO (1961):**

In response to growing concerns about drug safety, the World Health Organization (WHO) began to take an active role in coordinating global efforts to improve pharmacovigilance. In 1961, WHO established the Global Individual Case Safety Report (ICSR) System, a database for collecting and analysing reports of adverse drug reactions (ADRs) worldwide.

- **The Drug Regulation Act (1962):**

In the wake of the thalidomide crisis, the FDA, under the leadership of Dr. Frances Kelsey, passed the Drug Regulation Act of 1962 in the United States. The act significantly strengthened the FDA's authority to ensure the safety and efficacy of drugs before they were approved for public use.

4. The 1980s and 1990s: Formalization and Expansion

During the 1980s and 1990s, pharmacovigilance systems became more formalized, with the establishment of national and international regulatory frameworks to monitor drug safety.

- **FDA and EMA Role Expansion:**

In the 1980s, the FDA began to emphasize post-market drug safety surveillance, recognizing that adverse reactions could emerge only after a drug has been widely distributed. Similarly, the European Medicines Agency (EMA), established in 1995, took on a similar role in Europe, coordinating pharmacovigilance efforts across the European Union.

- **EudraVigilance System (2001):**

In 2001, the EMA introduced the EudraVigilance system, which allowed all member states of the EU to share information about ADRs. This system became an essential tool for monitoring the safety of drugs marketed within the European Union.

Safety Signals: EudraVigilance helps to detect and assess potential safety signals, such as new or rare ADRs, through data mining and signal detection tools. The system facilitates the rapid identification of new risks, ensuring that corrective actions can be taken.

- **VigiBase (1982):**

In 1982, the WHO's VigiBase system, initially set up to track individual case reports, evolved into a global repository of ADR data, receiving contributions from countries around the world. VigiBase became a vital source for identifying and analysing global drug safety signals.

- **International Conference on Harmonisation (ICH) (1990s):**

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), established in the 1990s, played a critical role in aligning regulatory practices worldwide. This collaboration between regulatory authorities (such as the FDA, EMA, and Japan's MHLW) and pharmaceutical industry stakeholders led to more standardized approaches for drug safety monitoring.

5. The 2000s: Technological Advances and Strengthening of Surveillance Systems

Advances in Technology:

The early 2000s saw significant technological advancements that improved pharmacovigilance systems. The increased use of electronic health records (EHRs), the internet, and data analytics allowed for more efficient collection and analysis of ADR data. Real-time reporting became possible, and the system became more proactive rather than reactive.

- ✓ **WHO's Pharmacovigilance Programme (2002):**

WHO's Pharmacovigilance Programme was established to monitor the safety of medications globally and ensure that drugs available for use worldwide are safe, effective, and of high quality.

- ✓ **The FDA's REMS (Risk Evaluation and Mitigation Strategies) (2007):**

In the U.S., the FDA introduced Risk Evaluation and Mitigation Strategies (REMS), which allowed the agency to require additional safety measures for drugs with known risks, such as restricted distribution systems or patient monitoring.

6. The 2010s to Present: Global Integration and Enhanced Pharmacovigilance Practices

Global Collaboration and Data Sharing:

Pharmacovigilance has become increasingly globalized, with databases like Vigibase (WHO), EudraVigilance (EMA), and MedWatch (FDA) sharing information across borders. The collaboration helps ensure that safety signals are detected early and mitigated more effectively.

✓ **The Role of Social Media and Big Data:**

The rise of social media and the use of big data in healthcare have transformed the landscape of pharmacovigilance. By analyzing online patient reports, social media platforms, and patient forums, regulators and researchers can now identify ADRs and trends more quickly. Additionally, data mining techniques are used to analyze large volumes of patient data for potential safety concerns.

✓ **Pharmacovigilance 2.0 - Artificial Intelligence and Machine Learning:**

The future of pharmacovigilance lies in Artificial Intelligence (AI) and Machine Learning (ML), which promise to revolutionize the way drug safety data is collected, analyzed, and interpreted. AI and ML are used to predict potential ADRs based on existing data and provide early warnings to prevent harm.

Global Pharmacovigilance Programs

Global pharmacovigilance programs play a crucial role in ensuring the safety of medicines worldwide. These programs are designed to detect, assess, understand, and prevent adverse drug reactions (ADRs) or any other drug-related problems that could harm public health. With the increasing number of drugs being approved and distributed globally, a robust pharmacovigilance system is necessary to monitor their safety throughout their lifecycle, particularly post-market.

The development of global pharmacovigilance programs has helped streamline drug safety monitoring and foster international collaboration in identifying safety signals, sharing information, and responding promptly to safety concerns.

1. World Health Organization (WHO) Pharmacovigilance Program

The World Health Organization (WHO) is one of the leading organizations responsible for coordinating global pharmacovigilance efforts. WHO provides a platform for global collaboration and the exchange of drug safety data among member countries. Key elements of WHO's pharmacovigilance program include:

✓ **WHO's Global Individual Case Safety Report (ICSR) System:**

Purpose: WHO collects and analyzes adverse drug reaction (ADR) reports from member countries to monitor the safety of medicines worldwide. This program provides a global database of individual case safety reports (ICSRs), which helps in identifying new safety signals and evaluating the benefit-risk profile of drugs.

✓ **Uppsala Monitoring Centre (UMC):**

WHO established the Uppsala Monitoring Centre (UMC) in Sweden in 1978, and it serves as the coordinating center for global pharmacovigilance. UMC supports the Vigibase system and offers expertise and training to national pharmacovigilance centers. It is also involved in research, data analysis, and the development of tools to improve drug safety monitoring.

2. European Medicines Agency (EMA) - Pharmacovigilance Program

The European Medicines Agency (EMA) is the central regulatory body responsible for monitoring the safety of medicines in the European Union (EU). EMA's pharmacovigilance program is an essential component of the European Union's drug safety system.

✓ **Pharmacovigilance Risk Assessment Committee (PRAC):**

The PRAC is an EMA committee responsible for the evaluation and management of risks related to medicines. It assesses the safety of medicines based on the data provided by EudraVigilance, conducts reviews, and recommends actions such as updating product information, issuing warnings, or withdrawing a drug from the market.

✓ **Collaboration with National Agencies:**

EMA collaborates with national pharmacovigilance centers across the EU, including those in the UK, France, Germany, and other member states. National agencies submit ADR reports to EudraVigilance and work with EMA to ensure timely action on safety concerns.

3. U.S. Food and Drug Administration (FDA) - MedWatch Program

In the United States, the Food and Drug Administration (FDA) is the regulatory authority responsible for overseeing the safety and effectiveness of medicines. The FDA's MedWatch program is a key component of its pharmacovigilance efforts.

✓ **MedWatch:**

Purpose: The MedWatch program is the FDA's primary system for monitoring the safety of drugs and medical devices in the U.S. healthcare system. It is a voluntary reporting system for healthcare professionals and the public to report adverse drug reactions (ADRs), side effects, and other drug-related safety concerns.

Post-Market Surveillance: MedWatch is a vital tool for post-market surveillance, allowing the FDA to detect safety signals that may not have been identified during clinical trials. The data collected through MedWatch helps the FDA evaluate whether additional regulatory actions, such as label changes or warnings, are necessary.

✓ **Collaborations and Data Sharing:**

The FDA works closely with other regulatory bodies, including EMA and WHO, to share data on drug safety and collaborate on risk management strategies. This helps ensure that global drug safety concerns are addressed and acted upon promptly.

4. National Pharmacovigilance Programs

Many countries have established their own pharmacovigilance programs to monitor drug safety within their borders. These programs are often coordinated with global initiatives like WHO and EMA, but they are tailored to the specific regulatory and healthcare needs of each country. Some examples include:

✓ **Pharmacovigilance Programme of India (PvPI):**

PvPI is the national pharmacovigilance program in India, which monitors the safety of medicines post-marketing. It is coordinated by the Central Drugs Standard Control Organization (CDSCO) and the Indian Pharmacopoeia Commission (IPC).

PvPI collects and evaluates ADR reports from healthcare professionals and the public, and it works in collaboration with the WHO's Uppsala Monitoring Centre and the VigiBase system. The program has significantly improved drug safety monitoring in India, with growing awareness and reporting of ADRs.

✓ **Japanese Pharmacovigilance Program:**

Japan's Pharmacovigilance Program is managed by the Pharmaceutical and Medical Devices Agency (PMDA). It includes extensive post-marketing surveillance of drugs and medical devices, which are closely monitored for any potential ADRs. Japan's program also includes data collection and signal detection through both voluntary and mandatory reporting systems.

5. Collaborative Efforts and Global Databases

As pharmacovigilance has become more integrated globally, collaborative initiatives and databases have emerged to enhance drug safety monitoring. Key international collaborations include:

✓ **The International Society of Pharmacovigilance (ISoP):**

ISoP is a global professional society that promotes pharmacovigilance by organizing conferences, workshops, and research initiatives. It encourages collaboration between regulatory bodies, pharmaceutical companies, and healthcare professionals to advance drug safety monitoring.

✓ **Pharmacovigilance Risk Communication:**

Global pharmacovigilance programs also emphasize risk communication. This includes disseminating safety information to healthcare professionals, patients, and the public through labelling updates, safety alerts, and educational campaigns.

Regulatory Bodies and Their Role in Pharmacovigilance

Pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) and other drug-related problems. Regulatory bodies play a crucial role in pharmacovigilance by establishing and enforcing policies and regulations to ensure the safety and efficacy of medicines throughout their lifecycle. These organizations monitor the safety of pharmaceuticals and medical devices in the market, respond to safety concerns, and ensure that necessary corrective actions are implemented.

4. Central Drugs Standard Control Organization (CDSCO) - India

Role in Pharmacovigilance: Regulation of Drugs in India: The Central Drugs Standard Control Organization (CDSCO), under India's Ministry of Health and Family Welfare, is the national regulatory authority responsible for ensuring the safety, efficacy, and quality of drugs and medical devices in India.

Pharmacovigilance Programme of India (PvPI): The PvPI is India's national pharmacovigilance program that monitors the safety of medicines after they are approved and marketed in the country. It collects, evaluates, and analyzes ADR reports and works closely with WHO's Uppsala Monitoring Centre to contribute to the global pharmacovigilance network.

National Coordinating Centre: The Indian Pharmacopoeia Commission (IPC) serves as the National Coordinating Centre (NCC) for PvPI. The NCC ensures the effective implementation of the pharmacovigilance program and coordinates with the state-level pharmacovigilance centers.

5. Medicines and Healthcare Products Regulatory Agency (MHRA) - United Kingdom

Role in Pharmacovigilance: Regulation in the UK: The Medicines and Healthcare Products Regulatory Agency (MHRA) is responsible for ensuring that medicines and medical devices in the United Kingdom are safe and effective. MHRA conducts pharmacovigilance activities, assesses the benefit-risk profiles of medicines, and monitors the safety of drugs after they are marketed.

Yellow Card Scheme: The Yellow Card Scheme is the MHRA's system for collecting reports of adverse drug reactions (ADRs) and medical device problems from patients, healthcare professionals, and the public. This system helps the MHRA detect potential safety concerns and take necessary regulatory actions.

6. Therapeutic Goods Administration (TGA) - Australia

Role in Pharmacovigilance: Regulation in Australia: The Therapeutic Goods Administration (TGA) is responsible for regulating medicines and medical devices in Australia. It monitors the safety of medicines both before and after they are marketed, ensuring they meet the required safety standards.

Importance of Post-Marketing Surveillance in Pharmacovigilance

Post-marketing surveillance (PMS) is a critical component of pharmacovigilance that focuses on the ongoing monitoring of the safety and efficacy of pharmaceutical products after they have been approved and made available to the public. It is an essential process that ensures that any adverse effects or safety concerns related to a drug, which may not have been identified during pre-market clinical trials, are detected, evaluated, and managed effectively. Post-marketing surveillance serves as a vital mechanism for maintaining public health and ensuring that approved medicines continue to meet safety and efficacy standards over time.

The importance of post-marketing surveillance can be highlighted in key areas (Figure 1):

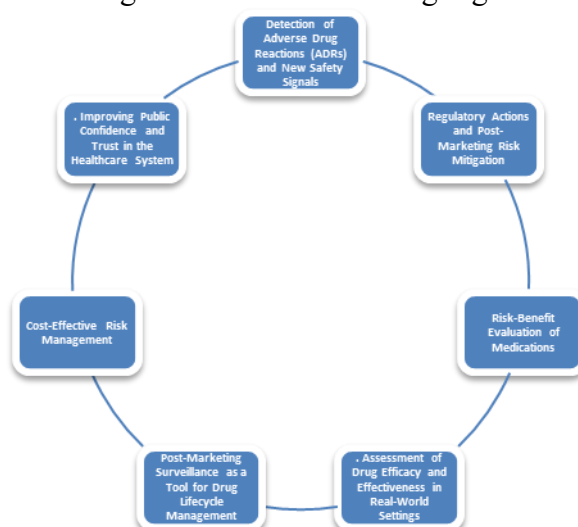


Figure 1: Pharmacovigilance cycle illustrating ADR detection, regulatory actions, risk–benefit evaluation, post-marketing surveillance, and public trust enhancement. The Indian Regulatory Landscape

The Role of CDSCO in Drug Safety

The Central Drugs Standard Control Organization (CDSCO) is the national regulatory authority responsible for ensuring the safety, efficacy, and quality of drugs and medical devices in India. It operates under the Ministry of Health and Family Welfare and plays a

critical role in drug safety by regulating the approval, manufacture, distribution, and monitoring of pharmaceuticals in the country. As the central authority for drug regulation in India, CDSCO's responsibilities include managing pharmacovigilance programs, monitoring the safety of medicines, and ensuring that drugs available in the Indian market meet the highest safety standards.

1. Pharmacovigilance and Drug Safety at CDSCO

Pharmacovigilance is a critical aspect of CDSCO's role in ensuring drug safety. As part of its mandate, CDSCO oversees the Indian Pharmacovigilance Programme, which monitors the safety of drugs after they have been released to the market. The main objective of this program is to detect, assess, and prevent adverse drug reactions (ADRs), which can occur after a drug has been approved and is widely used by patients.

Key Components of Pharmacovigilance by CDSCO:

- **Adverse Drug Reaction (ADR) Monitoring:** CDSCO monitors the occurrence of ADRs through a network of reporting centers across the country. This data is crucial for identifying potential safety concerns and managing the risks associated with pharmaceutical products.
- **Indian Pharmacovigilance Programme (PvPI):** In 2010, CDSCO launched the Pharmacovigilance Programme of India (PvPI) in collaboration with the Indian Pharmacopoeia Commission (IPC). PvPI aims to improve patient safety and ensure the safe use of medicines by collecting, assessing, and analyzing ADRs. The program provides a structured mechanism for healthcare professionals and patients to report ADRs and actively engages in the safety monitoring of drugs available in India.

2. The Role of CDSCO in the Indian Pharmacovigilance Programme (PvPI)

The Pharmacovigilance Programme of India (PvPI) is a national program coordinated by CDSCO, which plays a vital role in monitoring the safety of medicines and ensuring that ADRs are detected, reported, and assessed accurately.

Mechanism of ADR Reporting and Analysis:

- **Data Collection:** ADRs are reported through an online portal called the PvPI Portal. This portal allows healthcare professionals and patients to submit ADR reports in a standardized format.
- **Data Evaluation:** Once ADRs are collected, they are evaluated for potential safety concerns. The evaluation is done by experts at CDSCO and the IPC. Signals are detected and prioritized based on factors such as the severity of the reaction and the number of reported cases.
- **Risk Management:** If a safety concern is identified, CDSCO takes necessary regulatory actions, including advising healthcare providers, issuing drug safety warnings, or modifying the product's labeling to reflect the new information. In extreme cases, the drug may be withdrawn from the market.

4. Regulatory Actions by CDSCO in Drug Safety

When safety signals are detected through the pharmacovigilance system, CDSCO takes several regulatory actions to mitigate risks associated with medicines. These actions include:

- **Labelling Changes:** CDSCO can require pharmaceutical companies to update the labelling of drugs to include new safety information, such as newly identified adverse effects, contraindications, or warnings.

- **Issuing Safety Alerts:** CDSCO may issue safety alerts to healthcare professionals and the public regarding potential risks associated with a drug. These alerts may include guidance on how to manage specific ADRs or recommendations to discontinue use of the drug in certain populations.
- **Restricting Drug Use:** In cases where a drug poses significant risks, CDSCO may impose restrictions on its use. This could include limiting the drug to certain patient populations, reducing the recommended dosage, or requiring additional monitoring of patients using the drug.
- **Drug Withdrawal:** In extreme cases, when the risks of a drug outweigh its benefits, CDSCO may withdraw the drug from the market. This can happen if a previously unidentified or serious ADR is identified, or if safety concerns persist despite efforts to mitigate risks.

5. Challenges Faced by CDSCO in Drug Safety

Despite its critical role, CDSCO faces several challenges in ensuring drug safety in India. These challenges include:

- **Underreporting of ADRs:** One of the most significant challenges in pharmacovigilance in India is the underreporting of ADRs by healthcare professionals and patients. Many ADRs go unreported, leading to incomplete data on the safety of medicines.
- **Awareness and Training:** There is a need for greater awareness and training among healthcare providers, patients, and pharmaceutical companies about the importance of pharmacovigilance and ADR reporting.
- **Quality of Data:** The accuracy and quality of ADR data reported to the pharmacovigilance system can vary. Ensuring that reports are complete, accurate, and timely remains a challenge for CDSCO.

Pharmacovigilance Programme of India (PvPI)

The Pharmacovigilance Programme of India (PvPI) is a national initiative designed to monitor the safety of pharmaceutical products post-market, primarily focusing on the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs). Launched by the Central Drugs Standard Control Organization (CDSCO) in collaboration with the Indian Pharmacopoeia Commission (IPC) in 2010, the program plays a critical role in ensuring the safety of medicines used by the Indian population.

The aim of PvPI is to collect, evaluate, and analyze ADRs from drugs available in the Indian market to improve patient safety and ensure the availability of high-quality medicines. By systematically monitoring and reporting ADRs, PvPI contributes to improving the benefit-risk ratio of drugs, allowing for timely interventions and the reduction of harm associated with drug therapy.

1. Objectives of the Pharmacovigilance Programme of India (PvPI)

The PvPI has a clear set of objectives designed to improve pharmacovigilance practices in India and contribute to the global pharmacovigilance network:

- **To Collect ADR Reports:** The primary objective of the program is to gather information on adverse drug reactions (ADRs) from healthcare professionals, patients, and pharmaceutical companies.

- To Assess Drug Safety: PvPI evaluates the safety profiles of drugs in the Indian market by analyzing ADR data. This helps identify any potential risks associated with medicines, ensuring that their benefits outweigh the risks.
- To Strengthen Drug Safety Regulations: Through ADR reporting and analysis, PvPI helps regulatory authorities like CDSCO to take informed regulatory actions, such as drug recalls, label changes, or safety warnings.
- To Provide Education and Awareness: PvPI educates healthcare professionals and the public about the importance of ADR reporting. The program aims to raise awareness about pharmacovigilance and its role in ensuring drug safety.
- To Monitor the Post-Marketing Safety of Medicines: PvPI focuses on monitoring drugs once they are marketed to the public, identifying potential issues that might not have been apparent during clinical trials.
- To Contribute to Global Pharmacovigilance: PvPI also plays an active role in the WHO Programme for International Drug Monitoring (PIDM) by submitting ADR data to global databases, such as Vigibase, helping detect safety signals worldwide.

2. Structured Organization of PvPI

The Pharmacovigilance Programme of India (PvPI) operates under the guidance of CDSCO and is managed by the Indian Pharmacopoeia Commission (IPC). The structure of the program involves several key components:

- Indian Pharmacopoeia Commission (IPC): As the coordinating body, IPC is responsible for overseeing the implementation and management of PvPI. It provides technical support, guidance, and training for the program's operations.
- Pharmacovigilance Centres (PVCs): These are centers located at various hospitals, medical institutions, and healthcare organizations across India. PVCs are responsible for collecting and reporting ADRs to the central database, which is managed by IPC.
- National Coordinating Centre (NCC): The National Coordinating Centre (NCC) is based at the IPC and is responsible for coordinating the activities of PvPI across the country. It ensures that the ADR reports are processed, evaluated, and analyzed to detect safety signals.
- Health Care Professionals (HCPs): Doctors, nurses, pharmacists, and other healthcare professionals play an essential role in reporting ADRs. HCPs are the primary source of ADR data and are encouraged to submit reports through the PvPI system.

3. Mechanism of ADR Reporting in PvPI

The PvPI relies on the active participation of healthcare professionals, patients, and pharmaceutical companies for ADR reporting. The reporting process follows a structured mechanism, ensuring that all ADR reports are documented, analyzed, and acted upon.

- Reporting of ADRs: Healthcare professionals, patients, or caregivers can report any suspected ADRs using a standardized form (the Individual Case Safety Report (ICSR)). These reports can be submitted online through the PvPI website or directly to the nearest Pharmacovigilance Centre.
- Data Collection: Once ADRs are reported, the details are entered into a central database maintained by the IPC. The data includes information on the drug involved, the nature of the ADR, the patient's demographics, and the clinical outcomes.
- Data Evaluation: The ADR reports are evaluated for causality (whether the drug is the likely cause of the ADR) and severity. This is typically done using specialized tools like the Naranjo Algorithm or WHO-UMC Causality Assessment Scale.

- **Signal Detection:** If a pattern of ADRs is detected for a specific drug, this is considered a "signal." These signals are further analyzed to assess whether they represent a new or emerging safety concern.
- **Action and Feedback:** If significant safety concerns are identified, CDSCO and IPC take appropriate action, such as issuing safety warnings, revising drug labeling, or even withdrawing the product from the market. Feedback is provided to healthcare professionals, patients, and pharmaceutical companies.

4. Role of ADR Reporting in Improving Drug Safety

The Pharmacovigilance Programme of India (PvPI) contributes to improving drug safety through the collection and analysis of ADR reports. These reports help in detecting and assessing the risks associated with drugs once they have been marketed and used by a larger population.

- **Identifying Safety Issues:** ADR reports collected by PvPI help identify drugs that may have adverse effects that were not observed during clinical trials or are rare in nature.
- **Regulatory Interventions:** Through the analysis of ADR data, CDSCO can take timely regulatory actions, such as issuing advisories or mandating changes to drug labels, to protect public health.
- **Risk Communication:** PvPI helps communicate potential risks to healthcare professionals and the public, enabling informed decision-making regarding drug use.
- **Post-Marketing Surveillance:** PvPI serves as a tool for monitoring the long-term safety of drugs, especially in specific populations or when used in combination with other therapies.

5. The Importance of PvPI in India's Healthcare System

The Pharmacovigilance Programme of India (PvPI) is a crucial component of India's healthcare system, as it helps safeguard public health by ensuring that drugs available in the market are safe and effective. With the growing number of new drugs, biopharmaceuticals, and vaccines entering the Indian market, PvPI plays an important role in continuously monitoring their safety and addressing any emerging risks.

- **Patient Safety:** PvPI contributes directly to patient safety by ensuring that potential risks associated with medicines are identified and mitigated.
- **Global Drug Safety Network:** By submitting ADR data to global databases like VigiBase, PvPI contributes to international drug safety efforts, ensuring that drugs are safe not only in India but globally.

Structure and Operations of the Pharmacovigilance Programme of India (PvPI)

The Pharmacovigilance Programme of India (PvPI) is a national initiative designed to monitor the safety of pharmaceuticals available in the Indian market, focusing on the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs). It operates under the coordination of the Indian Pharmacopoeia Commission (IPC), which works in close collaboration with the **Central Drugs Standard Control Organization (CDSCO)**.

1. Structure of the Pharmacovigilance Programme of India (PvPI)

The Pharmacovigilance Programme of India (PvPI) is structured to involve multiple components and stakeholders who work together to monitor the safety of drugs and provide timely information regarding any safety concerns. The structure involves national, regional,

and local components, with key roles played by regulatory authorities, healthcare providers, and the general public.

1. National Coordinating Centre (NCC):

- ✓ The National Coordinating Centre (NCC) is the central authority responsible for overseeing the entire PvPI initiative. The NCC is located at the Indian Pharmacopoeia Commission (IPC) in Ghaziabad.
- ✓ The NCC coordinates the activities of all Pharmacovigilance Centres (PVCs) across India, manages the ADR reporting system, provides technical support, and ensures proper evaluation of ADR data.

2. Indian Pharmacopoeia Commission (IPC):

- ✓ The Indian Pharmacopoeia Commission (IPC) is the lead organization for managing PvPI. It is an autonomous body under the Ministry of Health and Family Welfare, Government of India.
- ✓ IPC acts as the National Coordinating Centre for PvPI and is responsible for setting guidelines, policies, and strategies for effective pharmacovigilance.
- ✓ It also provides training, awareness programs, and technical expertise to healthcare professionals and other stakeholders.

3. Pharmacovigilance Centres (PVCs):

- ✓ These are regional centres spread across India, located within hospitals, medical institutions, and healthcare organizations.
- ✓ PVCs collect and report ADR data, monitor the use of drugs, and ensure that ADR reports are submitted to the NCC in a timely and accurate manner.
- ✓ PVCs play a vital role in the grassroots collection of ADR information from healthcare professionals, patients, and pharmaceutical companies.

4. Patients and Consumers:

- ✓ Patients and consumers are also encouraged to report suspected ADRs. While healthcare professionals typically submit most ADR reports, the involvement of patients in reporting ADRs is essential for capturing a broader range of adverse events.
- ✓ Patients may report ADRs through online platforms or directly to healthcare providers, who can subsequently forward the information to PvPI.

5. Regulatory Authorities:

- ✓ The Central Drugs Standard Control Organization (CDSCO) is the apex regulatory body that oversees the approval, regulation, and monitoring of drugs in India. CDSCO works in close coordination with PvPI to take regulatory actions based on the safety data collected through the program.

2. Operations of PvPI

The operations of the **Pharmacovigilance Programme of India (PvPI)** focus on ensuring that any adverse drug reactions (ADRs) are reported, analyzed, and appropriately acted upon. The key operational components of PvPI include data collection, signal detection, ADR evaluation, risk assessment, and regulatory actions.

1. ADR Reporting:

- ✓ ADR reporting is the foundation of PvPI. The program encourages healthcare professionals, patients, and the pharmaceutical industry to report ADRs.
- ✓ Healthcare professionals submit ADR reports through the PvPI Portal, which is a web-based system maintained by the Indian Pharmacopoeia Commission (IPC).

- ✓ Patients can report ADRs via healthcare providers or directly through the online portal, allowing them to play an active role in pharmacovigilance.
- 2. **Data Collection and Submission:**
 - ✓ Once ADRs are reported, the data is collected, categorized, and submitted to the central database maintained by the Indian Pharmacopoeia Commission (IPC).
 - ✓ Data is structured in the form of Individual Case Safety Reports (ICSRs), which contain detailed information about the suspected ADR, the drug involved, patient demographics, and clinical outcomes.
- 3. **Data Analysis:**
 - ✓ The ADR data submitted by PVCs and other sources is carefully analyzed by the NCC and IPC for causality, severity, and clinical significance.
 - ✓ Causality assessment is performed using standardized tools such as the WHO-UMC Causality Assessment or Naranjo's Algorithm, which help determine whether the drug is likely responsible for the adverse event.
 - ✓ Severity is categorized as mild, moderate, or severe, based on the impact on the patient's health.
- 4. **Signal Detection:**
 - ✓ Signal detection involves identifying potential risks associated with a drug that might not have been apparent during clinical trials.
 - ✓ By analyzing the collected ADR reports, the PvPI can detect patterns that may indicate a safety concern.
- 5. **Risk Assessment and Evaluation:**
 - ✓ If a safety signal is confirmed, a risk assessment is carried out to evaluate the benefit-risk ratio of the drug.
 - ✓ The assessment involves analyzing the severity, frequency, and potential impact of the ADR, as well as considering factors like the therapeutic benefit of the drug and the population at risk.
- 6. **Reporting to International Databases:**
 - ✓ PvPI also plays an important role in contributing to the WHO Programme for International Drug Monitoring (PIDM), which helps share ADR data with other countries.
 - ✓ ADR data collected from India is submitted to Vigibase, the global ADR database managed by the Uppsala Monitoring Centre (UMC). This allows for international collaboration in drug safety monitoring and helps detect global safety signals.

3. Challenges in PvPI Operations

While PvPI has made significant strides in monitoring drug safety in India, several challenges remain:

- **Underreporting of ADRs:** One of the biggest challenges faced by PvPI is the underreporting of ADRs by healthcare professionals and patients. This leads to incomplete data and may delay the identification of safety concerns.
- **Data Quality and Timeliness:** Ensuring that ADR reports are accurate, complete, and submitted in a timely manner remains an ongoing challenge.
- **Awareness and Training:** Despite ongoing efforts, there is still a need for greater awareness and training among healthcare providers and the public about the importance of pharmacovigilance.

Indian Adverse Drug Reaction (ADR) Reporting System

The Indian Adverse Drug Reaction (ADR) Reporting System is a crucial component of the Pharmacovigilance Programme of India (PvPI). Its primary function is to collect, analyze, and manage information related to adverse drug reactions (ADRs) occurring post-market in India. The system helps identify potential safety concerns associated with medicines that may not have been apparent during clinical trials. Through the effective operation of this system, the safety of drugs is continuously monitored to protect public health.

The ADR reporting system in India is coordinated by the Indian Pharmacopoeia Commission (IPC), under the Central Drugs Standard Control Organization (CDSCO).

1. Structure of the Indian ADR Reporting System

The Indian ADR Reporting System is an integral part of the Pharmacovigilance Programme of India (PvPI). The system involves various components, including healthcare professionals, patients, hospitals, pharmaceutical companies, and regulatory bodies, all working together to ensure the timely collection and analysis of ADR reports.

1. Pharmacovigilance Centers (PVCs):

- ✓ These centers are located in hospitals, medical institutions, and healthcare organizations across India. PVCs act as the first point of contact for collecting ADR reports.
- ✓ Healthcare professionals (doctors, nurses, pharmacists) and patients submit ADR reports to the nearest PVCs, which are then forwarded to the National Coordinating Centre (NCC) for further analysis and action.

2. National Coordinating Centre (NCC):

- ✓ The NCC, located at the Indian Pharmacopoeia Commission (IPC), acts as the hub for coordinating all ADR-related activities in India.
- ✓ It consolidates the ADR reports submitted by the PVCs, ensures the proper analysis of data, and submits the data to international databases such as VigiBase (managed by the Uppsala Monitoring Centre, UMC) for global safety monitoring.
- ✓ The NCC also provides guidance to PVCs and ensures proper functioning of the ADR reporting system.

3. Healthcare Professionals:

- ✓ Doctors, nurses, pharmacists, and other healthcare professionals are the primary sources of ADR reports in India. They are encouraged to report any suspected ADRs related to pharmaceuticals, vaccines, or other therapeutic products.
- ✓ Healthcare professionals can report ADRs through the PvPI Portal, using an online system that allows easy submission of ADR data.

4. Patients and Consumers:

- ✓ Patients or consumers can report ADRs, either directly through healthcare providers or via dedicated ADR reporting systems. This enables the collection of reports from individuals who may experience adverse reactions but are not formally affiliated with healthcare institutions.
- ✓ Although healthcare professionals are the primary reporters, patient engagement in reporting ADRs is crucial for capturing a broader range of adverse events.

5. Pharmaceutical Companies:

- ✓ Pharmaceutical companies are legally required to report any ADRs related to their marketed products. They collaborate with the PvPI system and submit ADR data from clinical trials, post-marketing surveillance, and any adverse event information they receive from healthcare professionals or consumers.

2. ADR Reporting Process

The ADR Reporting Process in India follows a systematic and structured approach to ensure that adverse events are documented, analyzed, and acted upon in a timely manner.

1. Identification of Suspected ADRs:

- ✓ ADRs can be identified by healthcare professionals, patients, or pharmaceutical companies. In healthcare settings, doctors, nurses, and pharmacists report any adverse events they suspect might be related to a specific drug, vaccine, or therapeutic product.
- ✓ Patients can also recognize ADRs, and through reporting systems, they can help capture ADRs from the general population, ensuring a comprehensive data pool.

2. Submission of ADR Reports:

- ✓ ADR reports are submitted to the nearest Pharmacovigilance Centre (PVC). In healthcare institutions, ADR reports are typically compiled by the medical team and then forwarded to the appropriate PVC.
- ✓ ADRs can also be reported online through the PvPI Portal by healthcare professionals, patients, or pharmaceutical companies.

3. Data Entry and Documentation:

- ✓ Once an ADR report is submitted, the information is recorded in a standardized format known as the Individual Case Safety Report (ICSR). This report contains detailed information about the drug involved, the adverse event, the patient's demographic information, and clinical outcomes.

4. Data Evaluation and Analysis:

- ✓ The National Coordinating Centre (NCC) analyzes the ADR data to assess the causal relationship between the drug and the reported adverse event. Causality assessment is typically performed using tools like the WHO-UMC Causality Assessment and the Naranjo Algorithm.

5. Signal Detection:

- ✓ Signal detection involves identifying new or previously unknown risks associated with a drug that may not have been evident during clinical trials.
- ✓ If patterns of ADRs suggest a potential safety concern, these are flagged as signals, which are then subject to further evaluation.

6. Risk Assessment and Regulatory Action:

- ✓ Once a signal is confirmed, a thorough risk assessment is performed to determine the potential risk associated with the drug.
- ✓ If a significant risk is identified, regulatory actions may be taken, such as issuing safety advisories, updating drug labels with warnings, or in severe cases, withdrawing the drug from the market.

3. Role of ADR Reporting in Improving Drug Safety

The Indian ADR Reporting System plays a critical role in improving the overall safety of drugs by systematically identifying and addressing safety concerns that arise after drugs enter the market. Through active participation from healthcare professionals, patients, and pharmaceutical companies, the system contributes to:

1. Identifying New Safety Signals:

- ✓ Many adverse drug reactions are rare or may not be observed during pre-market clinical trials due to limited sample sizes or controlled conditions. The ADR reporting system helps identify these risks in a larger, more diverse population.

2. Improving Drug Safety:

- ✓ By continuously monitoring drugs after they enter the market, the ADR reporting system helps detect risks, assess the severity of adverse events, and take appropriate regulatory actions to ensure drugs remain safe for public use.

3. Regulatory Actions:

- ✓ Based on the information gathered through ADR reports, regulatory bodies like CDSCO can make informed decisions about drug safety, such as issuing safety alerts, updating drug labeling, or even withdrawing unsafe products from the market.

4. Global Collaboration:

- ✓ Through collaborations with international pharmacovigilance networks, India contributes to global drug safety monitoring. The sharing of ADR data with VigiBase enables global detection of safety signals, which can lead to global regulatory interventions.

Chapter 3: Drugs Discarded Globally But Still Available in India

Globally discarded drugs prevailing in India and the reason for their ban:

- **Metamizole** preferred for its analgesic action has been banned globally due to the risk of bone marrow depression and agranulocytosis.
- **Nimesulide** has been banned for paediatric use [below 12 years of age] in India on February 12, 2011, by the Union Ministry of Health and Family Welfare. This drug has been withdrawn due to fulminant hepatic failure in the year 2000 in various countries but is still being prescribed by some elder practitioners in India due to its par excellence in counteracting inflammatory pain.
- **Prophiphenazone** indicated for inflammatory pain has been discarded due to the adverse effect of bone marrow depression.
- **Nefopam**, the most preferred analgesic for post-operative pain, has been banned due to the higher incidence of occurrence of epilepsy.
- **Oxyphenbutazone**: This NSAID has been banned as it causes bone marrow depression.
- Some of the **paracetamol formulations** have been banned in a few countries due to analgesic abuse nephropathy. As such, combining paracetamol with other NSAIDs/other analgesics is considered to be irrational and such combinations are banned in a few countries, whereas in India, these formulations are still available.
- **Nitrofurazone**, available as an antibiotic cream, has been withdrawn due to its carcinogenic property.
- **Phenylpropranolamine**, prescribed for cold and cough, has been withdrawn due to its adverse effects such as dizziness and stroke.
- **Droperidol** used as an anti-psychotic has been banned as it causes irregular pumping of the heart.
- **Cerivastatin**, a hypercholesterolemia drug, has been withdrawn on account of rhabdomyolysis.
- **Phenolphthalein**, a laxative, has been discarded due to its carcinogenicity.
- **Cisapride** has been withdrawn due to the occurrence of irregular heartbeats.

- **Fenfluramine**, an anti-obesity drug, has adverse cardiotoxic effects.
- **Practolol** (banned in India too but still prescribed) has been banned due to adverse side effects like occulo-mucocutaneous syndrome and damage to lacrimal glands.[3,4,6,11,12]

Certain medications have been prescribed by doctors on a regular basis and have seen substantial growth in the Indian market. Although Nimesulide has been banned in India, some traditional doctors continue to prescribe it, possibly because they are unaware of the latest information on the medication. Analgin (metamizole) is produced and sold because of its superior pain-relieving qualities, but consumers are unaware of its negative side effects. Despite numerous bans in the Indian market, phenyl propanolamine (commercial examples: Vicks Action 500) is still widely used because of commercials featuring Kollywood and Bollywood celebrities. Additionally, because to analgesic abuse nephropathy, over-the-counter paracetamol formulations have been outlawed in Syria, Saudi Arabia, Bangladesh, Iran, and Kuwait; nonetheless, India continues to utilise them because of their superior antipyretic properties (Table 2).

Drugs	Indications	Reason for Ban
Diclofenac formulations (diclofenac + tramadol + chlorzoxacaine) (diclofenac + tramadol chlorzoxacaine + famotidine) (omeprazole paracetamol diclofenac) etc.	Analgesic	Liver Toxicity
Astemizole	Antihistamines	Prolonged QT interval
Terfenadine	Antihistamines	Prolonged QT interval
Phenformin	Antidiabetic	Lactic acidosis
Gatifloxacin.	Antibiotic (fourth-generation fluoroquinolones)	Diabetes mellitus
Rosiglitazone	Antidiabetic	Increased incidence of heart attack
Sibutramine	Antiobesity	Cardia arrhythmias and stroke
Rofecoxib	Selective COX-2 inhibitor	Increased incidence of MI and arrhythmias
Nimesulide	NSAIDS	Fulminant hepatic failure

❖ Case Study 1: Rofecoxib (Vioxx):

Introduction:

Rofecoxib was a popular nonsteroidal anti-inflammatory drug (NSAID) marketed under the brand name **Vioxx**. It was primarily used for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain. Developed by **Merck & Co.**, Vioxx was introduced to the market in 1999 and became widely prescribed due to its targeted mechanism of action as a **COX-2 inhibitor**. Unlike traditional NSAIDs, which inhibit both COX-1 and COX-2 enzymes, **COX-2 inhibitors** like Vioxx were believed to reduce inflammation while minimizing gastrointestinal side effects associated with non-selective NSAIDs.

The Global Withdrawal of Vioxx:

Despite its initial success, **Rofecoxib** (Vioxx) was withdrawn from the global market in September 2004. The decision to withdraw the drug came after **clinical trials** revealed serious safety concerns, particularly regarding cardiovascular risks. Specifically, the **VIGOR trial** (Vioxx Gastrointestinal Outcomes Research), which compared Vioxx with naproxen, found an increased risk of cardiovascular events, including heart attacks and strokes, in patients using Vioxx.

The **APPROVE trial** (Adenomatous Polyp Prevention on Vioxx), which was conducted to assess the role of Vioxx in cancer prevention, further confirmed these findings. The trial showed a significant increase in cardiovascular events among patients taking Vioxx, even in those who were considered at low risk for heart disease.

By the time of its withdrawal, an estimated **80 million people** worldwide had used Vioxx, and it was linked to tens of thousands of cases of heart attacks, strokes, and other serious cardiovascular events. The decision by **Merck & Co.** to voluntarily withdraw Vioxx from the market was influenced by the mounting evidence of cardiovascular risks and concerns over patient safety.

The Continued Availability of Rofecoxib in India:

Despite the global withdrawal of Vioxx, the drug continued to be available in India for some time. There were several reasons for this continued availability:

1. Delayed Regulatory Action:

- ✓ In India, the regulatory bodies, such as the Central Drugs Standard Control Organization (CDSCO), initially did not immediately take action following the global withdrawal of Vioxx. This delay in responding to the growing concerns regarding its safety meant that Rofecoxib remained available in the Indian market for a period after it was pulled from international markets.

2. Lack of Immediate Awareness:

- ✓ Although the safety issues with Vioxx were well-documented globally, the Indian healthcare system was not always as quick to disseminate critical safety information. There was a lag in communication regarding the cardiovascular risks associated with the drug, which delayed the recognition of the drug's dangers in India.

3. Differences in Regulatory Standards:

- ✓ Regulatory systems in different countries operate under different timelines and regulatory standards. While the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) acted promptly by withdrawing the drug from their markets, the Indian regulatory system took longer to evaluate the full scope of the safety concerns.
- ✓ Additionally, the economic implications of drug withdrawal in low- and middle-income countries (like India) can influence the pace of regulatory action.

4. Market Demand and Physician Preference:

- ✓ Despite global concerns, Rofecoxib was widely prescribed in India as an alternative to traditional NSAIDs. Its marketing and promotion, particularly its supposed gastrointestinal safety, created a strong demand among both physicians and patients.
- ✓ Many physicians in India continued to prescribe Vioxx, believing that it offered better gastrointestinal safety profiles compared to older NSAIDs. The reluctance to switch to alternative drugs contributed to the persistence of Rofecoxib in the Indian market.

5. Regulatory Actions in India:

The continued availability of **Rofecoxib** in India eventually prompted action from **CDSCO**. The regulatory body reviewed the global data on the cardiovascular risks of the drug and took the following steps:

1. Public Health Advisory:

- ✓ **CDSCO** issued a **public health advisory** to inform healthcare professionals about the risks associated with **Vioxx**. This included information on the increased incidence of cardiovascular events and recommended that healthcare providers exercise caution when prescribing COX-2 inhibitors.

2. Market Withdrawal:

- ✓ In response to the growing safety concerns and mounting international pressure, **CDSCO** initiated a phased withdrawal of **Rofecoxib** from the Indian market. By 2005, the drug was removed from pharmacies and healthcare settings across India.

6. Results from the Vioxx Case:

The **Rofecoxib (Vioxx)** case provides important lessons about drug safety, pharmacovigilance, and the role of regulatory agencies in protecting public health. Some key takeaways include:

- **Post-Marketing Surveillance is Critical:**

- ✓ The **Vioxx** case underscores the importance of **post-marketing surveillance** in detecting safety concerns that may not emerge during clinical trials. Drugs are often used by a much broader and diverse population post-approval, which can reveal rare or unforeseen side effects.

- **Global Collaboration in Drug Safety:**

- ✓ **Pharmacovigilance** should not be confined to national borders. The case of **Vioxx** highlights the need for **global collaboration** between regulatory bodies, healthcare providers, and patients. Early identification and communication of drug safety issues are essential for preventing widespread harm.

- **Timely Regulatory Action:**

- ✓ The delay in removing **Rofecoxib** from the Indian market illustrates how slow regulatory action can affect public health. Regulatory authorities need to act swiftly in response to safety signals, particularly when risks are well-established in international clinical trials.

- **Role of Healthcare Professionals in ADR Reporting:**

- ✓ Healthcare professionals play a critical role in **pharmacovigilance** by promptly reporting adverse drug reactions (ADRs) and safety concerns. Their vigilance can help identify emerging risks and contribute to timely regulatory interventions.

❖ Case Study 2: Fenfluramine (Fen-Phen)

Introduction:

Fenfluramine was a popular **appetite suppressant** used to aid weight loss, primarily prescribed for obesity management. It was often used in combination with **phentermine**, another appetite suppressant, in a regimen known as **Fen-Phen** (a portmanteau of fenfluramine and phentermine). **Fen-Phen** was widely prescribed during the 1990s as a weight-loss treatment, marketed as an effective solution for individuals struggling with

obesity. However, this combination therapy was later found to be associated with severe health risks, leading to its eventual withdrawal from the market.

Fenfluramine was marketed under various brand names, including **Pondimin** and **Isolamine**. The **Fen-Phen** combination became extremely popular due to its reported effectiveness in reducing appetite, helping users lose significant amounts of weight in a relatively short period.

The Emergence of Serious Health Risks:

Although Fen-Phen was initially celebrated for its weight loss efficacy, its use was not without significant risks. Over time, a series of adverse events linked to the drug combination began to emerge, culminating in its withdrawal from the market.

- **Cardiovascular Issues:** The most concerning and widely publicized side effects of Fenfluramine and Fen-Phen were **cardiovascular** in nature. There was growing evidence that the combination of fenfluramine and phentermine was linked to **pulmonary hypertension** (a rare and serious condition characterized by high blood pressure in the arteries of the lungs) and **valvular heart disease** (damage to the heart valves). These conditions were serious and potentially fatal, leading to life-threatening complications in patients.
 - ✓ **Pulmonary Hypertension:** Patients who had used Fen-Phen for an extended period developed pulmonary hypertension, a progressive disease that caused shortness of breath, fatigue, and in severe cases, heart failure. This condition was irreversible and often fatal.
 - ✓ **Valvular Heart Disease:** Fenfluramine was also associated with **valvular heart disease**, where the heart's valves become thickened and unable to function properly. This led to heart murmurs, fluid retention, and, in extreme cases, heart failure.
- **Fibrosis:** In addition to cardiovascular issues, Fenfluramine was also linked to **fibrosis**, a condition in which the tissues in the lungs, heart, and other organs become scarred and stiff, further exacerbating heart and lung problems.
- **Neurological Effects:** Though less common, some users reported neurological symptoms such as **dizziness**, **headaches**, **mood swings**, and **insomnia**, which were believed to be due to the drug's effects on serotonin levels in the brain.

The Role of Post-Marketing Surveillance and Reporting:

The **adverse effects** associated with Fen-Phen began to emerge slowly, but as more patients reported issues and data started to be compiled, a **signal** of potential harm became apparent. This situation exemplifies the critical role of **post-marketing surveillance** and the need for continuous monitoring of drugs after they enter the market. Early warning signs included reports of patients experiencing **heart valve damage** and **pulmonary hypertension**, but these adverse events were not immediately linked to Fen-Phen use.

Pharmacovigilance efforts were crucial in identifying these risks and triggering further investigations. Patients, healthcare providers, and researchers played a pivotal role in reporting suspected adverse reactions, which helped raise awareness of the issue. The discovery of the link between Fenfluramine and heart disease prompted **the U.S. Food and Drug Administration (FDA)** to take regulatory action.

Regulatory Response and Market Withdrawal:

The mounting evidence from clinical studies and ADR reports led to increased scrutiny by regulatory bodies:

- **FDA's Action:** In September 1997, the **FDA** requested that the manufacturer of **Fenfluramine** and **Dexfenfluramine** (a related drug) voluntarily withdraw these medications from the market. This followed reports of serious health risks, including the development of **valvular heart disease** and **pulmonary hypertension** among long-term users. The FDA's decision to ask for the drug's withdrawal was a response to growing concerns over its safety profile.
- **Legal and Financial Consequences:** Following the withdrawal of Fenfluramine, **Merck & Co.** faced numerous **lawsuits** from individuals who had suffered adverse effects from using Fen-Phen. The financial burden of these lawsuits, combined with the damage to the company's reputation, led to significant legal settlements.

The Continued Availability of Fenfluramine in India:

Despite the global withdrawal of Fenfluramine and its combination with phentermine (Fen-Phen), it remained available in certain countries for a longer period, including in India. There are several reasons for this:

1. Regulatory Delays in India:

- The Indian regulatory authority, **CDSCO (Central Drugs Standard Control Organization)**, was slower to respond to the global concerns regarding Fenfluramine and Fen-Phen. It took several years after the withdrawal in Western markets before India initiated any regulatory measures. This delay resulted in Fenfluramine being available for a longer period in India, exposing more patients to potential harm.

2. Economic and Market Factors:

- Weight loss drugs, including Fenfluramine, were marketed aggressively in India, where **obesity** and **overweight** issues were becoming increasingly prevalent. Fen-Phen's effectiveness in promoting weight loss made it a sought-after option for patients and healthcare professionals, even in the face of safety concerns.

The Impact of the Fen-Phen Case on Drug Regulation:

The **Fenfluramine (Fen-Phen)** case provided several important lessons for the field of **pharmacovigilance** and drug safety, highlighting the need for stronger regulatory frameworks and enhanced post-marketing surveillance.

- **Enhanced Post-Marketing Surveillance:**
 - ✓ The case of Fenfluramine underscores the importance of **post-marketing surveillance**. Even after a drug has passed through clinical trials and is approved for use, it is crucial to continue monitoring its safety once it is available to the general population. Adverse effects that may not have been detected in pre-marketing trials may emerge only when the drug is used by a larger, more diverse group of patients.
- **Global Coordination:**
 - ✓ Regulatory bodies worldwide, including the **FDA**, **EMA**, and **CDSCO**, must communicate and coordinate their actions more effectively to prevent delays in recognizing and addressing safety issues associated with drugs marketed internationally. In the case of Fenfluramine, the delay in regulatory action in certain countries, such as India, contributed to continued harm to patients.

❖ Case Study 3: Nimesulide

Introduction:

Nimesulide is a **non-steroidal anti-inflammatory drug (NSAID)** that is commonly used to treat pain and inflammation, particularly in conditions like osteoarthritis, rheumatoid arthritis, and dysmenorrhea (painful menstruation). It was developed by **BGP Products** in the 1980s and marketed by **Rhone-Poulenc Rorer** (now part of Sanofi). Nimesulide is available in various forms, including tablets, suspension, and topical formulations. It is known for its relatively fast action in relieving pain and inflammation, which made it a popular choice for physicians and patients.

Initial Market Success and Global Popularity:

Nimesulide became widely used in the 1990s, especially in countries across **Europe, Asia, and Latin America**, due to its effectiveness in treating pain and inflammation. Its relatively favorable side-effect profile compared to traditional NSAIDs (such as **ibuprofen** and **diclofenac**) led to its popularity. Because Nimesulide primarily inhibits **COX-2**, it was thought to have a lower risk of causing gastrointestinal side effects such as ulcers or bleeding, which are commonly associated with **COX-1 inhibitors** (like older NSAIDs).

The Rise of Safety Concerns:

While Nimesulide was marketed as a safer NSAID, its safety profile soon came under scrutiny due to reports of serious adverse events, particularly related to **liver toxicity**. Several cases of **hepatotoxicity** (liver damage) and **liver failure** were reported, leading to concerns about the drug's safety, particularly for long-term use.

- **Hepatotoxicity:**

- ✓ One of the major safety issues with Nimesulide was its potential to cause **liver toxicity**, including **hepatitis**, **liver failure**, and **jaundice**. In some severe cases, liver failure was fatal, leading to a high level of concern among healthcare professionals and regulatory bodies.
- ✓ **Liver injury** associated with Nimesulide was found to be dose-dependent in some patients, while others developed symptoms after relatively short-term use, suggesting that **individual susceptibility** also played a role in the severity of adverse reactions.

- **Risk of Severe Adverse Reactions:**

- ✓ Other adverse reactions linked to Nimesulide included **kidney damage**, **gastrointestinal problems**, and **allergic reactions** such as skin rashes.

Regulatory Responses and Market Withdrawals:

As reports of severe liver damage began to accumulate, regulatory bodies in various countries initiated investigations into the safety of Nimesulide.

- **European Union:**

- ✓ The **European Medicines Agency (EMA)** issued a warning in the early 2000s regarding the risks associated with Nimesulide. In 2007, following a review of available safety data, the EMA recommended the suspension of Nimesulide's marketing in some countries due to concerns over liver toxicity.
- ✓ In countries like **Ireland, Italy, and France**, Nimesulide was heavily regulated and its use was restricted.

- **India:**

- ✓ Despite the global concerns and restrictions, Nimesulide remained available in the **Indian market** for several years. The **Central Drugs Standard Control Organization (CDSCO)**, the regulatory body in India, took a more cautious approach to banning the drug. Although there were reports of hepatotoxicity, the drug

continued to be sold and prescribed for conditions like **fever, dysmenorrhea, and musculoskeletal pain.**

- ✓ Nimesulide's use was common in paediatric populations for fever management, despite warnings regarding its safety, particularly for children. In fact, Nimesulide was frequently prescribed for **fever** in infants and young children in India, which was a cause for concern given the potential liver toxicity.
- **Latin America:**
 - ✓ In countries such as **Brazil, Mexico, and Argentina**, Nimesulide was also widely used. However, after safety concerns arose, regulatory bodies in some Latin American countries began imposing restrictions or withdrawing Nimesulide from the market, following in the footsteps of European regulatory authorities.
- **Other Regions:**
 - ✓ Countries like **the United States** never approved Nimesulide for marketing, mainly due to concerns about liver toxicity and the lack of data supporting its safety for long-term use.

Continued Use in India Despite Global Concerns:

Despite the global withdrawal of Nimesulide in several countries, it continued to be widely used in **India**, where it was often prescribed as a first-line treatment for pain and fever in both adults and children. There are several reasons for this continued use:

1. Delayed Regulatory Action:

- The **CDSCO** did not act swiftly in regulating Nimesulide, even after the increasing evidence of adverse reactions and global withdrawals. This delay in response contributed to its continued availability in the market.

2. Economic Considerations:

- Nimesulide was an **affordable** option for pain management in India, and its lower cost made it an attractive alternative to other more expensive NSAIDs. Additionally, its effectiveness in reducing pain and fever contributed to its widespread use.

3. Marketing and Availability:

- Nimesulide's aggressive marketing by pharmaceutical companies and its availability over-the-counter (OTC) in some regions further contributed to its prolonged use. Physicians often prescribed the drug based on patient demand, which perpetuated its presence in the market.

The Role of Pharmacovigilance in the Nimesulide Case:

The Nimesulide case emphasizes the importance of **pharmacovigilance** in monitoring drug safety and identifying risks after a drug has been approved for use. While pre-marketing clinical trials provide valuable data on a drug's safety profile, it is only after the drug enters the market that real-world safety data becomes available. The role of **post-marketing surveillance** and **adverse drug reaction (ADR) reporting** in this case was crucial for identifying the risks associated with Nimesulide, particularly its **hepatotoxicity**.

• **ADR Reporting and Monitoring:**

- The early identification of **liver toxicity** as a significant side effect of Nimesulide was due to the efforts of healthcare providers, patients, and regulatory authorities who reported adverse events. This data played a pivotal role in triggering further investigations into the drug's safety.

The Decision to Limit or Withdraw Nimesulide in India:

In 2011, after years of monitoring and safety concerns, the **Central Drugs Standard Control Organization (CDSCO)** took action and **restricted the use of Nimesulide in India**. Key regulatory actions included:

- **Restriction to Adult Use:** Nimesulide was restricted to use in **adults** only, with a clear contraindication in **children** under the age of 12, particularly due to the risk of liver toxicity.
- **Short-Term Use Only:** The drug was allowed for **short-term use only** (up to 15 days) and was contraindicated in patients with pre-existing liver conditions or a history of liver disease.
- **Stricter Guidelines for Prescribers:** Healthcare professionals were advised to prescribe Nimesulide only when absolutely necessary and after considering alternative pain management options.

Despite these restrictions, the drug continued to be prescribed in certain regions of India, leading to concerns that proper enforcement of these guidelines was necessary to prevent potential liver damage among patients.

Why globally discarded drugs still prevail in India:

The continued availability of certain drugs that have been discarded globally, such as **Rofecoxib**, **Fenfluramine**, and **Nimesulide**, in India can be attributed to several key factors. These factors are a combination of regulatory challenges, economic considerations, gaps in public awareness, and the complexities of the healthcare system in India. Understanding these reasons is crucial for improving drug safety and pharmacovigilance in the country.

1. Regulatory Delays and Gaps in Enforcement

- **Slower Regulatory Response:** In many cases, Indian regulatory bodies, such as the **Central Drugs Standard Control Organization (CDSCO)**, have been slower to respond to global safety concerns and initiate recalls or restrictions on drugs. While countries like the **United States**, **European Union**, and **Japan** acted swiftly to remove or restrict these drugs, CDSCO took longer to issue a formal ban or impose severe restrictions. This delay allowed the continued availability of certain drugs in the Indian market.
- **Lack of Coordination with Global Agencies:** India's regulatory agencies often lack coordination with global health authorities, such as the **FDA** and **EMA**, in the implementation of safety measures. This leads to delays in recognizing and acting upon safety concerns raised in international studies, which in turn affects the timely withdrawal of potentially harmful drugs.

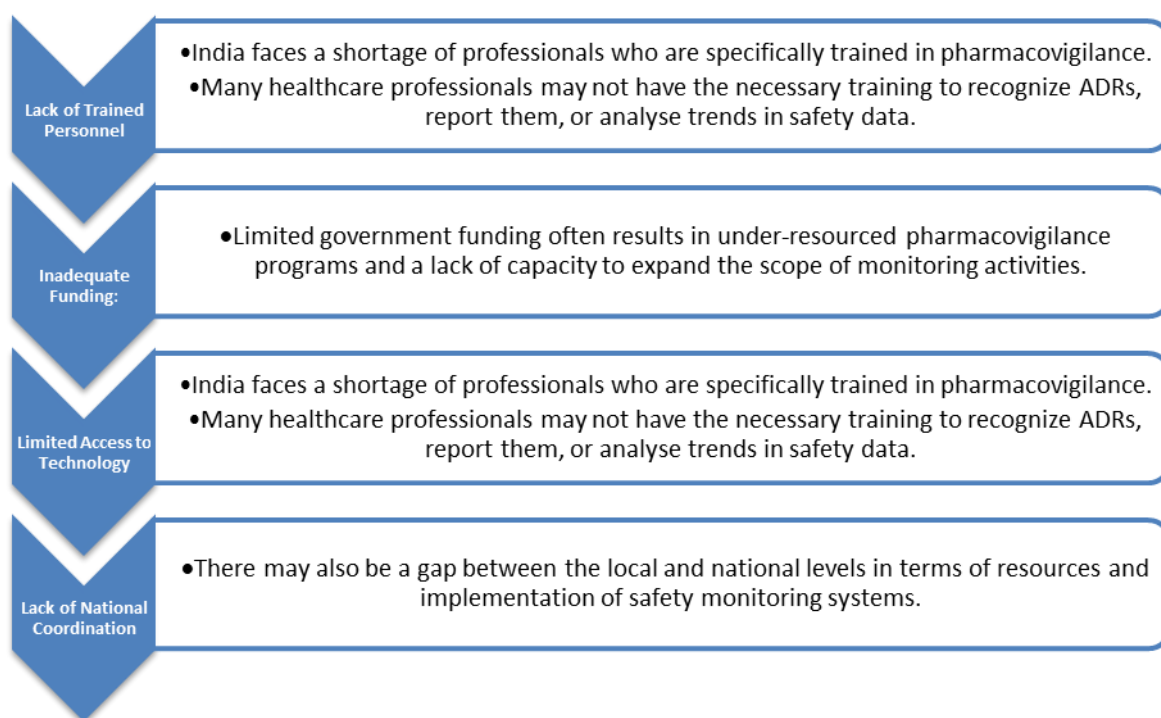
2. Economic and Market Considerations

- **Cost-Effectiveness:** Many of the drugs in question, such as **Nimesulide**, remain affordable options for patients in India. These drugs are often marketed as **low-cost alternatives** to newer, more expensive medications. This affordability makes them attractive options in a country with a large population of individuals who may not have access to more costly treatments.
- **Wide Market Demand:** Drugs like Nimesulide and Rofecoxib have a substantial user base in India due to their **perceived efficacy** in treating common conditions like pain and inflammation. These drugs are widely prescribed and consumed, especially for conditions like **osteoarthritis**, **dysmenorrhea**, and **headaches**. Due to the demand

for these drugs, pharmaceutical companies continue to market them, despite concerns about their safety profiles.

3. Limited Public Awareness and Education

- **Lack of Awareness Among Healthcare Providers:** In some cases, **healthcare providers** in India may not be fully aware of the latest global safety concerns regarding certain drugs. Many medical professionals may continue to prescribe these drugs based on their familiarity, perceived efficacy, and historical use.
- **Public Ignorance:** In some instances, patients may not be fully aware of the risks associated with certain drugs, particularly if those drugs have been marketed heavily and are widely accepted within the healthcare system. **Patient education** about the potential side effects of these drugs, especially in the case of **Nimesulide**, which has been linked to liver toxicity, is often lacking.
- **Misleading Marketing Campaigns:** Pharmaceutical companies often continue to market drugs with claims that emphasize their benefits while downplaying or ignoring the potential risks. This can lead to the widespread use of such drugs in India, as patients and healthcare providers may be influenced by these marketing strategies.



4. Influence of the Pharmaceutical Industry

- **Pharmaceutical Lobbying:** The **pharmaceutical industry** in India plays a significant role in shaping drug policies and regulations. Strong lobbying from pharmaceutical companies that manufacture and distribute these drugs can delay regulatory action.
- **Lack of Strong Regulation on Marketing Practices:** In India, the **regulation of pharmaceutical marketing** is often weaker compared to developed nations. Companies can continue promoting drugs that have been banned or restricted in other countries, leading to the continued availability of such drugs in the market.

5. The Complexity of Health Needs in India

- **Large and Diverse Patient Population:** India has a **large and diverse population**, with significant disparities in healthcare access, education, and socioeconomic status. For many patients, access to affordable medication is a priority, and the availability of cheaper drugs, even those with known risks, can be a major factor in their use.
- **Increased Use of Self-Medication:** In some cases, patients in India may engage in **self-medication**, particularly with over-the-counter drugs. This is common with drugs like **Nimesulide**, which is often available without a prescription.

BLACK BOX WARNINGS

The FDA issued black box warnings to vigilant healthcare professionals about serious ADRs. (Black box is a terminology) “Black box” is a term that states to the datum that at the starting point of the package insert of the drug there is factually a black box encircling the written warning to attract the attention of the purchaser. The FDA newly made a strenuous effort to embrace more black box warnings on more products to upsurge public safety[13] Table 3.

Drug Class	Indication	Black Box Warning
Antipsychotics	Psychosis, schizophrenia, depression, bipolar disorders	The mortality rate was high in geriatric patients with dementia-related psychosis
Fluoroquinolones	Bacterial infections	Tendon rupture
Opoids	Analgesic	Abuse liability, acute respiratory depression
Beta-agonist	Asthma and COPD	Increased risk of mortality
SSRIS	Depression	Suicidal thinking among adolescents
Valproic acid	Seizure	Liver toxicity
Amiodarone	Arrhythmias	Lung and liver toxicity
Second-generation anticoagulants	Atrial fibrillation	Spinal and epidural hematoma
Erythropoiesis stimulating agents	Anemia in CKD, chemotherapy, HIV	Stroke and venous thromboembolism

DISCUSSION

Suggestions regarding improvement of drug safety in India:

A few commendations to augment drug safety in India comprise the following:

- 1) Prescribing a medication for which ADR information is available.
- 2) Providing adequate information to patients when new drugs have been prescribed, sensitizing them regarding probable ADRs, and approval of novel drugs with attention to diseases for which safe substitutes are already present.
- 3) Exhibiting banned drugs in pamphlets and newsletters in every pharmacy will play a major role in creating awareness among the general population.
- 4) Creating awareness by the NPP regarding banned drugs and establishing a committee by the DTAB to regulate banned drugs with severe ADRs; also, the NPP should work on creating a positive attitude among healthcare professionals so that reporting about ADRs becomes an acknowledged and continuous practice.
- 5) Creating awareness about ADR reporting and introducing reporting methods for patients will enormously intensify the reporting of cases. A concurrent verification process can be

implemented to authorize that the ADR reported by the patients is potentially associated with the use of a particular drug.[14]

Recommendations and Future Directions

As India continues to grow as a global player in the pharmaceutical industry, enhancing drug safety through robust pharmacovigilance systems is essential. While significant progress has been made, there is still a long way to go to ensure that drugs on the market are safe, effective, and closely monitored for long-term health outcomes. This chapter outlines recommendations and future directions for improving drug safety in India, focusing on policy recommendations, technological innovations, strengthening international regulatory collaboration, and emerging trends in pharmacovigilance.

1. Policy Recommendations for Improving Drug Safety in India

India has a well-established framework for pharmacovigilance under the Pharmacovigilance Programme of India (PvPI), but there are several areas that need strengthening. The following policy recommendations can further enhance drug safety in India:

1.1 Strengthen ADR Reporting Systems:

The underreporting of adverse drug reactions (ADRs) continues to be a major challenge in India. To address this, policies should focus on:

- Simplifying the reporting process: Encouraging healthcare professionals and the public to report ADRs through user-friendly digital platforms and mobile apps.
- Training programs: Mandatory training for healthcare professionals in recognizing ADRs and understanding the importance of reporting these events.
- Incentivization: Providing incentives for healthcare providers who report ADRs regularly, including certification or rewards.

1.2 Improve Regulatory Frameworks and Response Time:

India's drug regulatory authorities, particularly the Central Drugs Standard Control Organization (CDSCO), need to expedite the drug safety review process. Key measures include:

- Faster drug approval and withdrawal procedures: Establish clear and transparent guidelines for quicker regulatory responses to ADR reports, and streamline the processes for product recalls and safety labelling changes.
- Regular updates to drug safety regulations: Ensure that the regulatory framework adapts to new scientific evidence and global pharmacovigilance practices.

1.3 Promote Public Awareness and Engagement:

To enhance public engagement in pharmacovigilance, policies should encourage:

- Public education campaigns: Launch national campaigns to raise awareness about the importance of ADR reporting and the role of the public in pharmacovigilance.
- Community-based outreach: Partnering with local healthcare facilities and community leaders to educate patients about the risks associated with medicines and how to report ADRs.

1.4 Strengthen Post-Marketing Surveillance

There is a need to enhance post-marketing surveillance in India. Policies should focus on:

- Increased funding for long-term studies: Promoting research on long-term safety monitoring of drugs, particularly those that are widely prescribed in India.
- Real-world evidence (RWE) studies: Encouraging the collection and analysis of real-world data to track adverse events that may not have been evident in clinical trials.

2. Technological Innovations in Pharmacovigilance

Technology has the potential to revolutionize pharmacovigilance by improving data collection, signal detection, and regulatory responses. Here are key technological innovations that can enhance drug safety monitoring in India:

2.1 Artificial Intelligence (AI) and Machine Learning (ML):

AI and ML can be utilized to improve the detection of adverse drug reactions and predict potential safety issues by:

- Analyzing vast amounts of ADR data from multiple sources like social media, electronic health records (EHRs), and healthcare databases to identify trends and emerging safety signals.
- Automating the detection of ADR signals from large datasets, helping regulatory bodies and pharmaceutical companies act more quickly and efficiently.

2.2 Big Data Analytics:

By harnessing big data from various health sources, pharmacovigilance can be more robust. Big data can provide insights into:

- Real-time monitoring of adverse drug reactions using data from health insurance claims, electronic health records, patient registries, and clinical trials.
- Predictive modeling to anticipate safety risks based on previous data and pattern recognition.

2.3 Blockchain Technology:

Blockchain can ensure the integrity and transparency of pharmacovigilance data. It can:

- Enhance traceability: Every ADR report can be securely recorded on a decentralized platform, making the data tamper-proof and transparent.
- Streamline data sharing: Blockchain can facilitate secure cross-border sharing of ADR data between global regulatory authorities and stakeholders, improving international collaboration.

2.4 Mobile Health (mHealth) Applications:

mHealth applications can support pharmacovigilance efforts by allowing patients and healthcare providers to easily report ADRs. These apps can:

- Collect real-time ADR reports directly from users and healthcare providers.
- Provide users with drug safety information, warnings, and recommendations on how to manage ADRs, improving awareness and proactive drug safety management.

2.5 Artificial Intelligence for Signal Detection:

AI can be used to develop advanced signal detection algorithms that are capable of identifying previously unknown adverse events. The use of AI in pharmacovigilance will increase the speed and accuracy of safety signal detection, leading to quicker regulatory interventions.

3. Strengthening International Regulatory Collaboration

Global collaboration is essential to ensure the safety of medicines, especially as the pharmaceutical industry becomes increasingly international. Strengthening cooperation with international organizations will enhance pharmacovigilance in India. Key steps include:

3.1 Active Participation in Global Pharmacovigilance Networks:

India should continue to strengthen its participation in global pharmacovigilance networks such as:

- VigiBase: Contributing ADR data to the WHO VigiBase to enhance global signal detection and safety monitoring.
- International Conference on Harmonisation (ICH): Working with global regulators to align national policies with international standards for drug safety and regulation.

3.2 Enhanced Data Sharing and Transparency:

India should enhance data sharing agreements with international partners and adopt transparent reporting practices by:

- Sharing ADR data with global databases: Regularly contributing to global safety databases like VigiBase, FDA Adverse Event Reporting System (FAERS), and EMA's EudraVigilance.
- Collaborating on cross-border pharmacovigilance initiatives: Promoting transparency and cooperation in managing the risks of drugs marketed in multiple countries.

3.3 Strengthening Harmonization of Regulatory Standards:

India should align its regulatory standards with international frameworks such as:

- Good Pharmacovigilance Practices (GVP): Adopting international standards for post-marketing surveillance and pharmacovigilance activities.
- International Regulatory Forums: Participating in discussions and collaborations with agencies like the FDA, EMA, and WHO to harmonize drug safety regulations and response protocols.

3.4 Collaborating in Safety Alert Mechanisms:

India can benefit by working with international regulatory bodies to:

- Issue joint safety alerts and recalls in cases where drugs pose a significant risk.
- Collaborate on public health communications to ensure patients and healthcare professionals are promptly informed about drug safety issues.

4. Future Trends in Drug Safety and Pharmacovigilance

The landscape of pharmacovigilance is evolving rapidly, driven by advances in technology, changes in global regulations, and the increasing complexity of drug therapies. The following trends are expected to shape the future of drug safety:

4.1 Personalized Medicine and Pharmacovigilance:

With the rise of personalized medicine, pharmacovigilance will increasingly focus on the individual characteristics of patients, including genetic, environmental, and lifestyle factors. This will require:

- Tailored risk assessments: Identifying specific ADRs that may be more likely in certain genetic profiles or patient populations.
- Increased precision in ADR detection: Utilizing genomic and molecular data to predict and monitor adverse drug reactions more effectively.

4.2 Real-Time Pharmacovigilance:

The future of pharmacovigilance will likely be real-time. With advances in digital health, regulators will be able to track the safety of medicines continuously, identifying ADRs as they occur. This will be made possible by:

- Big data analytics that process real-time data from electronic health records, wearables, and mobile apps.
- Continuous monitoring of drugs in the market using electronic health tools, providing more up-to-date safety information to healthcare providers.

4.3 Artificial Intelligence and Predictive Pharmacovigilance:

AI will continue to play a major role in predicting potential ADRs before they become widespread. By analyzing large datasets, AI will be able to:

- Identify unknown safety signals and predict long-term adverse effects of drugs based on patterns and trends observed in real-world data.
- Improve signal detection algorithms to flag potential risks more accurately and quickly than current methods.

4.4 Globalized Drug Safety Networks:

As global pharmaceutical markets continue to expand, the need for international collaboration in pharmacovigilance will increase. Future efforts will focus on:

- Harmonizing regulations between emerging markets like India and established markets.
- Expanding access to pharmacovigilance data globally, ensuring better decision-making for drug safety.

4.5 Post-Market Drug Surveillance for Biologics and Biosimilars

As biologic drugs and biosimilars become more prevalent, post-market surveillance will become even more critical. Pharmacovigilance practices will need to adapt to track the safety of these complex therapies, which may have different risk profiles compared to traditional small-molecule drugs.

CONCLUSION

In order to keep them up with the knowledgeable citizens of developed nations, it is important to inform and educate the general public about internationally prohibited drugs and the risks involved in using them, as well as to raise awareness among clinicians and other healthcare professionals about the severe adverse reactions of prohibited medications: The establishment of drug information centres can help achieve these goals by providing consumers and healthcare professionals with logical, objective, and critically evaluated information about the medications. [3]

teaching undergraduate medical students about prohibited substances in order to prevent future prescriptions of such medications. The Drug Controller General of India must first assess a new drug's efficacy and safety before introducing it to the market. [4,5] Even now, the prohibition process is still in place in India, giving manufacturers plenty of time to make new drugs due to the strict enforcement of laws by regulatory bodies (DTAB and DCGI) to move quickly and creatively to discard medicines when they are determined to be harmful to consumers. The last drug-bannencing body in India, DTAB, is set to firmly revoke the licenses of pharmacists who keep illegal substances in large quantities. In order to conduct proper and regular inspections of drug dispensing facilities, this need requires the appointment of more drug inspectors. [15,16]

More drug inspectors must be hired in order to do accurate and frequent inspections of drug dispensing outlets. [15,16]

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