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**Review**

# A Comprehensive Overview On Pharmacovigilance Ensuring Drug Safety

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## Abstract

In order to guarantee medication safety, enhance clinical procedures, and safeguard the public's health, pharmacovigilance is essential in identifying and controlling adverse drug reactions (ADRs). Expert systems are crucial for quickly detecting safety issues and averting product withdrawals because to the increasing amount of ADR data. Complex, cross-border safety issues can be better managed by implementing independent review methods and fortifying the worldwide pharmacovigilance network, such as through the Uppsala Monitoring Center. The creation of pharmacovigilance centers around the world has strengthened medication safety monitoring, despite ongoing issues including underreporting and data quality. Initiatives since the year 2000 have concentrated on enhancing drug safety systems, encouraging cooperation between researchers, healthcare providers, and regulatory bodies, and extensively sharing safety data. Pharmacovigilance developments have changed the strategy from changing from reactive to proactive, filling in the gaps, and enhancing medication safety. Along with lowering patient harm and promoting sensible prescription usage, these advancements have also increased confidence in healthcare systems around the world. Pharmacovigilance is becoming a vital instrument for public health protection.

**Keywords:** Pharmacovigilance, Drug safety, Adverse Drug Reactions, Public health, Safety

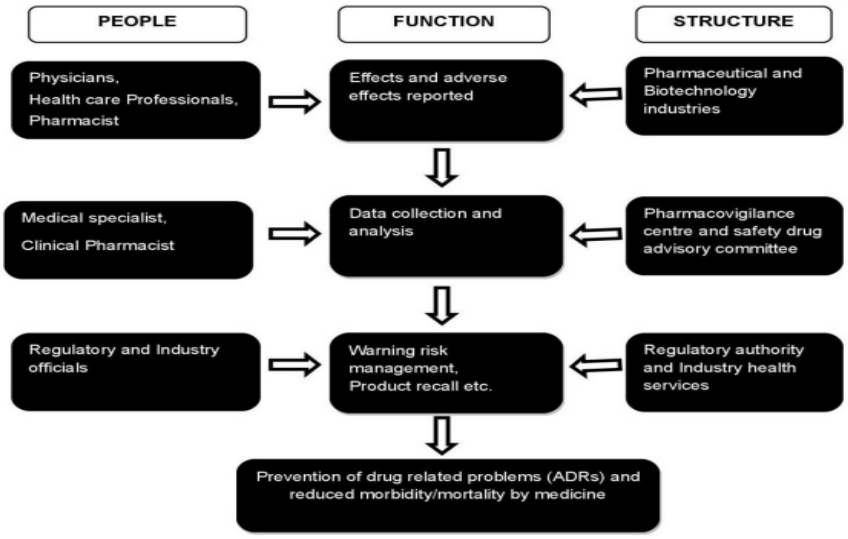
## INTRODUCTION

Pharmacovigilance and drug safety remain prominent clinical and academic areas. The World Health Organization (WHO) identifies pharmacovigilance as "the science and efforts regarding the identification, evaluation, comprehension, and avoidance of side effects or any other drug-related issue;(1) The "Programme for

International Drug Monitoring," a pilot attempt initiated by the World Health Organization (WHO) in 1968, planned to accumulate worldwide data regarding adverse drug reactions (ADRs). In Particularly, identifying the earliest relevant PV proofs were the primary goal of the "WHO Programme." A French group of toxicologists and pharmacologists coined the word PV in the middle of the 1970s to describe the actions supporting "The assessment of the risks of side effects potentially associated with drug treatment". (2) It is necessary to ensure certain patients and physicians have been given sufficient information to make the right choice of drug for treatment. (3) In order to detect risks and stop harm, pharmacovigilance entails monitoring and assessing adverse effects of drugs, vaccines, and medical devices. To preserve patient safety and trust among the public, pharmaceutical companies must actively track drug safety throughout the lifespan of a medicine. (4) However, despite all of these advantages, research shows that larger adverse drug reactions—which are frequent but frequently avoidable—occur in both developed and poor nations attitudes and views regarding influence, results, and advantages and disadvantages. (5) PV is especially worried about adverse drug reactions (ADRs), which are unpleasant and unexpected reactions to drugs that occur at dosages typically used for illness diagnosis, treatment, or prevention or to alter physiological function. (6) For optimal benefits and decrease threats, it is essential to constantly assess the effects of drugs. In order to ensure the safety of drugs throughout its duration under regulatory monitoring, post-marketing pharmacovigilance employs methods such as data mining to identify adverse drug responses. (7) In the process of medication safety monitoring, there are many different partners ,including the government, business, healthcare facilities, hospitals, academic institutions, medical and pharmaceutical societies, and toxins. These relationships are complex and crucial media, patients, consumers, health professionals, and information centers (8-10). A strong pharmacovigilance system is essential given India's expanding involvement in international drug development. Strong PV standards are necessary to monitor and control adverse drug reactions globally as Indian businesses develop and introduce new medications locally as well as internationally.

**Scope of PV**

Since 1972, pharmacovigilance has grown the ability to effectively evaluate and coordinate side effects in order to manage the dangers associated with current medications. By incorporating safety into clinical practice and policy, it ensures that both patients and healthcare providers apply drugs safely. (11) A typical setup for PV studies, including people involved on various levels, organizational units and their functions are shown in Figure:




**History of PV**

Over 65 nations have their own pharmacovigilance facilities in 2002. Coordination of WHO International Drug Monitoring membership is done by the Uppsala Monitoring Center (UMC), which is the WHO Collaborating Center for International Drug Monitoring. Effective clinical practice currently relies heavily on pharmacovigilance, which is founded on solid scientific concepts. To satisfy the needs of contemporary public health and public expectations, the field must advance. A resolution was adopted at the Sixteenth World Health Assembly (WHA 16.36). (12) 5] that eventually resulted in the establishment of the WHO and reiterated the necessity of prompt action with relation to the quick distribution of information on adverse medication reactions. An international drug monitoring pilot project the goal was to create a method that could be used globally to identify previously unidentified or poorly understood side effects of medications. (13)

**Vaccines and Biological Medicines**

Since vaccines are often administered to healthy youngsters, they need specific safety monitoring. Because of the high standards for safety, even small issues might jeopardize vaccination programs, influencing adherence and increasing the chance of illness recurrence. It is still difficult to establish causal relationships with unfavorable situations.(14,15) For instance, vaccinations are administered to the majority of the nation's birth cohort at an age when coincidental disease is likely to occur, and information on dechallenge and recchallenge is frequently lacking.

It's likely that multiple vaccinations will be given at the same time. the potential for programmatic mistakes to occur during vaccination handling, administration, storage, or transportation. Nonetheless, the regulatory body's accountability extends far beyond ensuring the safety of vaccinations used in immunization campaigns. You should never ignore mistakes, One example of a programmed error is a medical event brought on by no means limited to the safety of vaccines used in immunization programs.

Effective biological product regulation is essential to preventing harm to the public from poor storage or manufacturing practices. Safety issues, such as blood product contamination and threats including hepatitis B, HIV, and vCJD, emphasize the necessity of stringent regulation.(16) Pharmacovigilance must improve donor selection, screening, and sterilization in order to address safety concerns in products generated from plasma. Large-scale clinical studies are required to guarantee the safety of biological medications, hence proficiency in virology and microbiology is essential.

**Pharmacovigilance in Drug Regulation**

Partnerships with regulators strengthen pharmacovigilance programs. Regulators are aware that pharmacovigilance is essential to maintaining continuous safety of pharmaceuticals.

***Clinical trial regulation:***Clinical practice must incorporate strong safety monitoring due to the increase in clinical studies. Patient care is improved and medication-induced risks are identified through training medical personnel, sharing data among PV centers, and integrating safety research with health policy. (17)

**Clinical trials in INDIA**

India's clinical research space and prospects are highly appealing, which has made it a favorite location for clinical trials for multinational pharmaceutical companies (18). Clinical trials in India have the following benefits:

> Adherence to US FDA and ICH-GCP guidelines.
> Competent research specialists who speak English.
> Assistance and collaboration from the government.
> Less expensive than in Western nations. (19)
> Prevalence of diseases that are relevant worldwide.
> Robust system and enhanced patent laws (since 2005).
> Scientific viability, medical infrastructure, cost competitiveness, and commercialization potential are the main drivers of growth. (20)

Indian contract research companies (CROs) are excellent because of their extensive understanding of investigator sites, cost effectiveness, and local experience. (21,22) The expansion of clinical research in India's main therapeutic areas is fueled by favorable rules, GCP awareness, and a diversified patient base. (23)

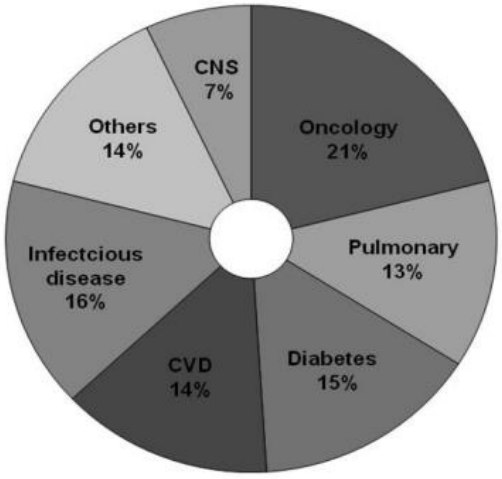



**Fig 2: Clinical trials that are outsourced to India are distributed according to therapeutic areas.**

**SWOT Analysis of Indian Clinical Trial Sector**

***Advantages***

-Large population (16% of the world's population, 1.2+ billion).
-Robust biotech and pharmaceutical sectors with highly qualified workers.
- With 500 distinct active medicinal compounds, they are the third-largest companies globally.
- Fourth in the world, accounting for 8% of the world's pharmaceutical output. (25)
-Government programs that encourage innovation.
- Due to the big population, there is a lot of data mining about the safety profile of pharmaceuticals. (26)

***Weaknesses***

-Low health sector expenditure: 2.1% of budget, 0.35% of GDP (2009-10). (27)
-Developed countries spend significantly more (e.g., US: 16%, France: 11%).
- Insufficient funds to execute nationwide initiatives such as PV. (28)

***Opportunities***

-With 4635 recognized communities, it is the largest repository of human biodiversity and is perfect for researching genetic variation and medication efficacy.
-300+ medical, 230+ dentistry, 830+ pharmacy, and 650+ nursing schools offer a strong potential for a competent labor force. (29)

***Threats***

-ADRs are not being reported.
-Limited financial resources.
- ADR monitoring centers are reduced.

***Post marketing safety drug monitoring***

Pharmacovigilance includes comparing safety profiles of medications, identifying drug interactions, evaluating the safety of inactive components, and tracking the effects of drug residue. The benefit-risk assessment report from The Council for International Organisation of Medical Sciences (CIOMS) has enhanced post-marketing assessments of medication efficacy and safety. (30)

Many ADRs go unnoticed despite the FDA's strict screening because of small, skewed clinical trials. Post-market monitoring is essential since premarketing testing does not accurately represent real-world use. PV guarantees ongoing safety testing of newly created medications. (31,32) Pharmaceutical firms must contend with fierce rivalry and stringent regulatory reviews, which necessitate intricate R&D procedures. After a medicine is introduced to the market, post marketing PV uses special data sources to guarantee its safety. (33) The WHO describes "signals," which are unproven connections between a drug's effects on the human body and possible side effects, as the foundation of PV research. These indicators aid in identifying medication-related dangers. (34) Spontaneous Reporting Systems (SRS), which are already in place in certain European and American countries, are used by academics and physicians to generate extensive signal databases. Other approaches are also investigated, such as post-market research and database analysis of general practitioners. However, the majority of data is still unavailable to researchers, which restricts the ability to discover signals.(35-37) Drug manufacturers keep track of adverse occurrences, but doctors are responsible for detecting them. In addition to other post-drug inputs, researchers are developing methods to evaluate ADR data from various sources.(38) For the benefit of businesses, regulators, and researchers, PV researchers use data and text-mining of medical records to create tools that enhance drug evaluations. (39)

***Pharmacovigilance in national drug Policy***

It is the duty of national governments to provide high-quality, safe, and effective medications and to ensure that they are used appropriately. Governments,particularly important is multidisciplinary collaboration; connections must be made between the various health ministry departments as well as with other stakeholders, including the pharmaceutical industry, academic institutions, nongovernmental organizations (NGOs), and professional associations in charge of educating the public about pharmacotherapy monitoring and rational medication use. (40)

***Pharmacovigilance in Disease Control Public Health Programmes***

Medicine safety monitoring is frequently an issue in areas with weak regulatory frameworks or healthcare facilities. This is particularly true in regions that are fighting tropical diseases like tuberculosis, HIV/AIDS, and malaria. Lack of real-time pharmacovigilance (PV) systems in these settings can hinder treatment results by delaying the identification of adverse drug reactions (ADRs). (41)To guarantee medication safety and effectiveness, efficient PV systems must be established. PV is a priority for public health programs around the world since improving drug safety in these susceptible groups requires international cooperation and training of medical personnel.

**Pharmacovigilance and International Health**

An independent review method could improve the Uppsala Monitoring Center's worldwide pharmacovigilance network to handle serious drug safety issues that could affect public health internationally. A methodology for gathering, evaluating, and disseminating information about drug safety concerns is outlined in the Erice Declaration. The burden of ADRs is still high despite improvements in pharmacovigilance, and pharmacoeconomic research shows that governments bear a heavy financial burden from ADR-related medical bills. (42) Sociopolitical, economic, and cultural factors also impact the safety profile of medications by influencing public attitudes, consumption habits, and availability to medications.

***Drug utilization***

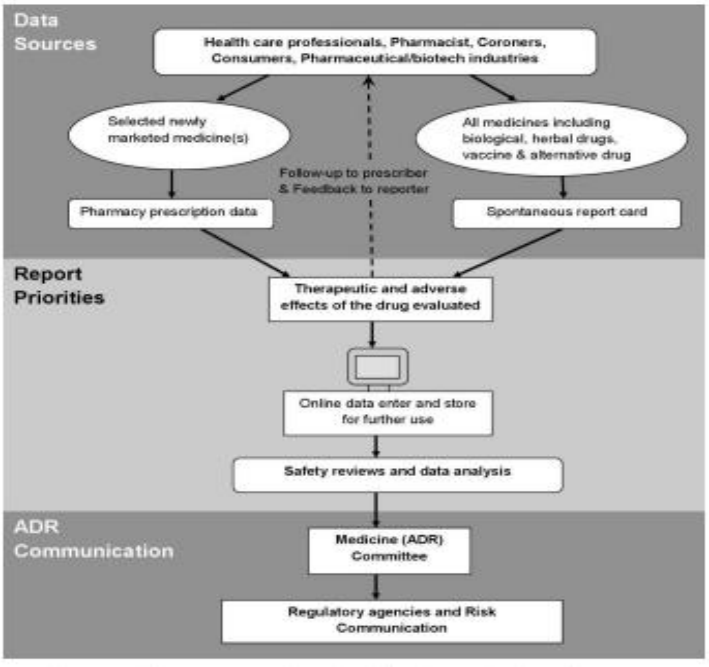
Drug safety is greatly influenced by drug use patterns, with injectable medications being more prevalent in developing nations. enhanced self-medication, illegal internet drug sales, and overprescription have resulted from consumers' enhanced ability to make therapeutic decisions without the assistance of a doctor or pharmacist due to the rise of direct-to-consumer advertising. Through collaborations with the media, educational institutions, and organizations, public health initiatives should concentrate on increasing awareness among patients as well as the wider public, including young people and the elderly. National pharmacovigilance centers are essential to the functioning of WHO's International Drug Monitoring Program, and ideally, each nation should have one. (43)

**PV in INDIA**

Pharmacovigilance (PV) and ADR surveillance were relatively late concepts in India. It wasn't until 1986 that certain doctors, mostly from academic institutions, pushed for more awareness of the possible negative effects of prescription medications and sensible prescribing, which led to the establishment of the concept of monitoring medications for side effects. As a result, the first ADR monitoring program was established, with 12 regional centers, however it was a failure. When India joined the WHO Adverse Drug Reaction Monitoring Programme, which is headquartered in Uppsala, Sweden, in 1997, significant progress was made. Three ADR monitoring facilities were established, mostly in teaching hospitals.

A National Pharmacovigilance Center at the Department of Pharmacology, AIIMS, New Delhi, as well as two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital), marked the beginning of India's early attempts to set up a pharmacovigilance system. The purpose of these centers was to track adverse drug reactions (ADRs) and notify the Indian drug regulating body of them. However, because of inadequate government financing and prescribers' ignorance of ADR reporting, they were inoperable. Consequently, the attempt was unsuccessful. To address these concerns, the World Bank-funded National Pharmacovigilance Program (NPVP) for India was introduced in 2005, with support from the WHO. (44)

The Central Drugs Standard Control Organization's (CDSCO) National Pharmacovigilance Advisory Committee oversaw the National Pharmacovigilance Program (NPVP), which was introduced in January 2005. The program's two zonal centers, North-East (New Delhi) and South-West (Mumbai), were in charge of gathering ADR data across the country and sending it to the committee and the Uppsala Monitoring Center in Sweden.



Fostering a reporting culture, involving healthcare professionals in the distribution of information, and establishing the program as a global benchmark for drug monitoring were the three primary goals of the initiative. In the end, the program failed in spite of their efforts. (45)

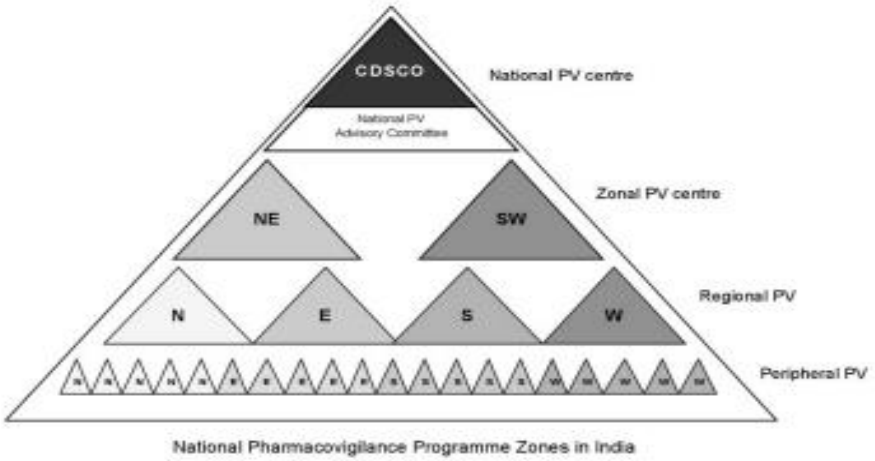



**Fig 3: National Pharmacovigilance Program zone structure**

***Current PV Program in India***

Government of India, Ministry of Health and Family Welfare (MoHFW), 2011. Strengthening ADR surveillance and guaranteeing medication safety nationwide were the goals of the Pharmacovigilance Programme of India (PVPI). 22 ADR monitoring facilities, including AIIMS in New Delhi, were set up as part of this project. The program's objective was to protect public health by methodically gathering, evaluating, and tracking ADR reports. A more comprehensive strategy for executing and growing the program was adopted with the transfer of the National Coordination Centre (NCC) to MoHFW. (46)

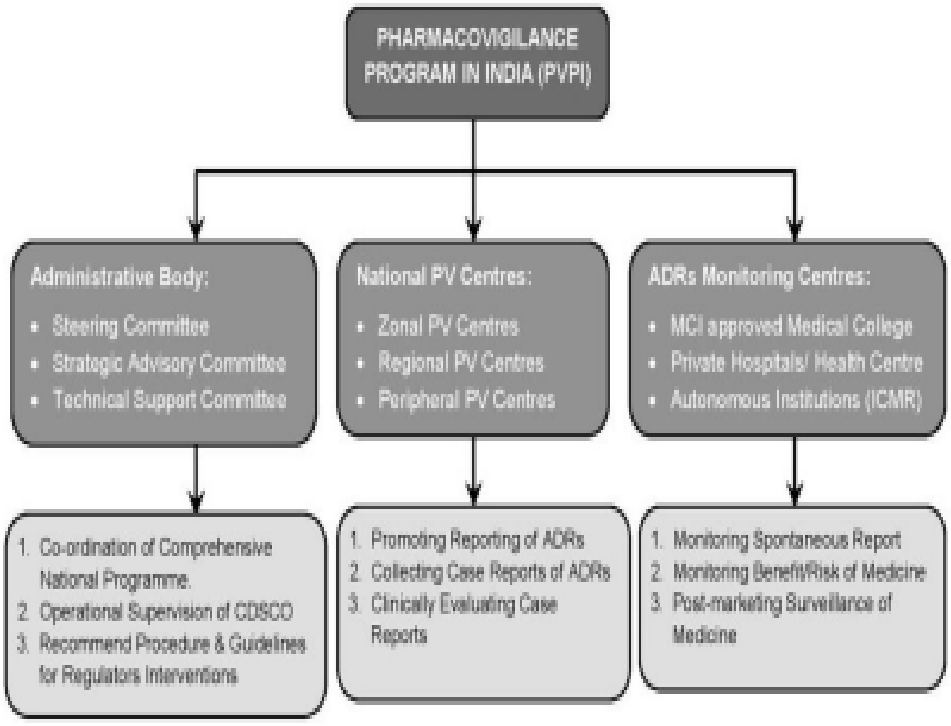



**Fig 4: Pharmacovigilance program in India and responsibilities.**

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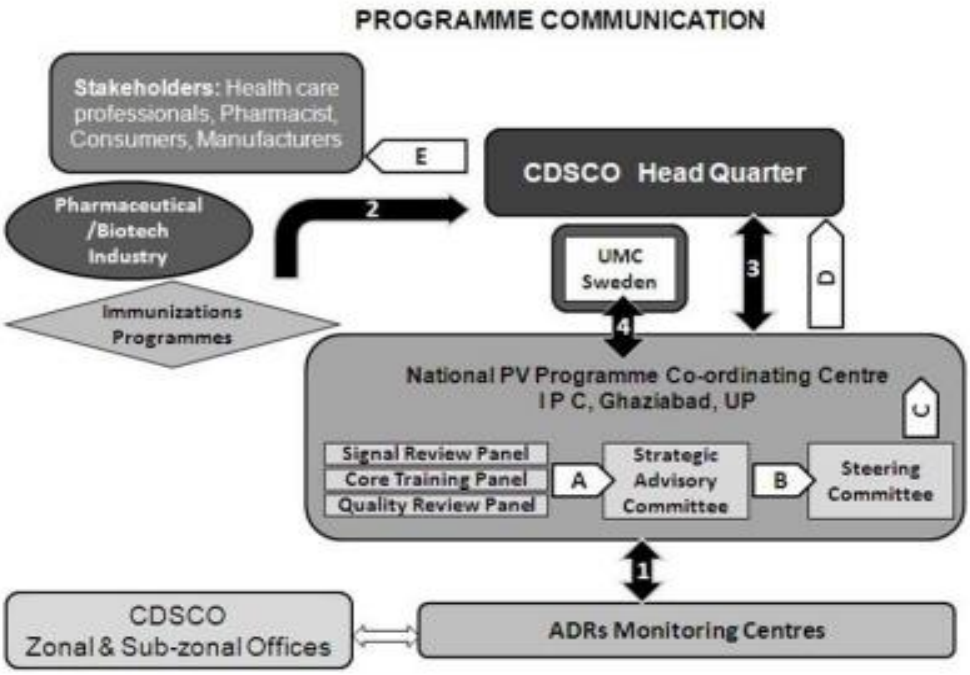


**Fig 5: ADR data Program Communications**

***ADR data flow***

Pharmacovigilance (PV) personnel gather ADR reports at the ADR Monitoring Centers (AMCs), verify their accuracy, and do initial causality analyses. The coordinating center receives these reports, does additional causality analysis, and uploads the information to the PV database. The coordinating center incorporates PV operations into public health initiatives and regularly prepares aggregated ADR reports. (47) For signal processing, the ADR data is sent to the Uppsala Monitoring Centre (UMC) via the VigiFlow interface. The correctness of the data is guaranteed by a quality review panel, and centers are evaluated according to performance indicators like training and report completeness.

**The Challenges of PV in India**

One of the issues facing the Pharmacovigilance Programme of India (PVPI) is the underreporting of adverse drug reactions (ADRs), which is caused by a lack of medical knowledge, qualified personnel, and public awareness across the country. Outdated infrastructure and protracted regulatory delays are further problems. India should work with IT professionals to develop a strong system for monitoring ADRs and guaranteeing medication safety in order to make improvements. ADRs frequently go unnoticed, which can have serious consequences and raise medical expenses. (48) As India's pharmaceutical industry expands and makes research and development investments, better safety evaluations for new medications are required. Therefore, DCGI needs to make some difficult choices and pledge to impose PV as a requirement and establish a PV inspection culture.

**Future prospects**

To identify new ADRs and support regulatory actions to safeguard the public's health, pharmacovigilance (PV) systems must advance. In order to help patients and healthcare providers make better decisions, information sharing should be prioritized. Patients should be a major source of data for PV in the future. For drug safety and regulatory compliance, the DCGI needs to enhance PV. Innovative tools for effective ADR detection are being used by companies such as GlaxoSmithKline; better PV practices should follow suit.

**The Erice Declaration**

By calling on public health organizations, medical professionals, the pharmaceutical industry, regulators, the media, and consumers to maintain the highest ethical and scientific standards in order to ensure the safe use of medications, the Erice Declaration promotes pharmacovigilance. It urges governments and decision-makers to be open and honest when informing the public and patients about the advantages, dangers, and efficacy of medications.

**Challenges for the Erice Declaration**

***Communication Difficulties:*** Inconsistent safety messaging, particularly in vaccination campaigns, can erode public confidence and coverage.

***Transparency:*** Open communication of facts, numbers, and decision-making procedures is necessary since secrecy undermines confidence.

***Regulatory Communication:*** To quickly address global issues, national drug regulators and pharmacovigilance centers need to communicate more effectively.

**International Response to Drug safety Issues**

A coordinated international response is necessary because some medication safety issues can have serious global health repercussions. The World Health Organization (WHO) has backed the creation of an impartial advisory group in this area, comprising epidemiologists, academics, regulators, and clinical pharmacologists. The purpose of this panel is to advise WHO on matters of safety pertaining to pharmaceuticals. The panel assists in informing member states about these safety concerns through WHO's Collaborating Centre for International Drug Monitoring, guaranteeing a unified and knowledgeable worldwide approach to drug safety. (49)

**Considerations for the Future and its Challenges**

Some of the major issues that pharmacovigilance programs will face over the next 10 years, briefly outlining the possible effects of these trends on the development of the scientific method.

Here are some important things to think about going forward that could be enhanced to create better pharmacovigilance practices:

1. Pharmacovigilance should concentrate more on expanding our understanding of safety than on identifying harm.
2. Formal decision analysis can be applied to complex risk-benefit decisions and is likely to improve them.
3. A culture of scientific advancement should guide pharmacovigilance. This calls for a stronger academic foundation, more accessible basic training, resources devoted to scientific strategy, and the proper balance of contributions from other disciplines.
4. Pharmacovigilance procedures and results should be systematically audited.

Some Major challenges face pharmacovigilance are as follows:

***Globalization***

The expansion of drug distribution worldwide and the growing exposure of vast populations to high dosages of medications. Among these are new chemical substances that are utilized for symptomatic alleviation, lifestyle changes, and medications used in underdeveloped nations to reduce the occurrence of pandemic diseases like TB, HIV/AIDS, and malaria. (50).

***Web-based sales and information***

In addition to its many advantages, the Internet has made it easier for medications to be sold illegally across international borders. All types of drug information are disseminated, with differing degrees of accuracy globally using this channel. Prescription medications, unregistered medications, highly regulated compounds, and conventional and herbal remedies with dubious safety, effectiveness, and quality are all covered by this material.

***Broader safety concerns***

As the variety of pharmaceuticals increases, so does the reach of pharmacovigilance. It is now understood that medication safety encompasses more than just the tracking, identifying, and evaluating adverse drug reactions (ADRs) that take place within a given dosage range and under precisely defined circumstances. Instead, it is intimately related to societal drug use habits. Pharmacovigilance addresses issues related to irrational drug use, overdoses, polypharmacy and interactions, the growing use of herbal and traditional medicines in combination with other medications, the illegal online sale of medications and drugs of abuse, the rise in self-medication, subpar medications, medication errors, and lack of efficacy. For current systems to effectively handle this wide scope, they must change. (51)

***Public health versus pharmaceutical industry economic growth***

The pharmaceutical sector may have flaws and may have competing interests when it comes to public health challenges brought on by problems with drug safety. The industry must address its shortcomings in post-marketing surveillance and clinical trial safety monitoring.

***Monitoring of established products***

The pharmaceutical industry's generic division is not entirely aware of its obligation to consistently check the safety of its goods all around the world. Even when generic medications interact with other medications, there

is a mistaken notion that they are always safe. The biggest provider of necessary medications is the generic industry.

***Attitudes and perceptions to benefit and harm***

These developments have fundamentally altered how society uses medications. Patients, healthcare professionals, and the public has reacted to these shifting tendencies in a variety of ways. In light of these quick advancements, their assessment of the advantages and disadvantages of medications as well as the acceptable risk level have not been adequately taken into account. It has been demonstrated that medications can cause serious harm. Only recently have industrialized and developing nations acknowledged the importance of drug-induced illness morbidity and mortality on their public health agendas. (52)

***Outcomes and Impact***

In addition to growing public knowledge of medication safety, people are also paying more attention to how well the medical community and industry are performing. as well as authorities. More studies on the efficacy of pharmacovigilance and its role in enhancing public perception must follow from increased accountability. Giving medical professionals and patients themselves relevant information that enhances individual treatment, facilitates the detection and treatment of illnesses brought on by medication, and overall lowers the incidence of iatrogenic diseases must be a top priority.

## CONCLUSION

Pharmacovigilance (PV), which addresses the issues of medication safety that regulators, producers, and medical practitioners face, is crucial for public health in India. India needs knowledge and coordinated strategies like pharmacogenomics to be a worldwide leader in pharmaceuticals. By recognizing, disclosing, and controlling side effects, PV promotes responsible and safe drug use. It informs regulatory decisions, fosters patient trust, and informs medical professionals on the advantages and hazards of drugs.

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