Pharmacovigilance: History and development in india

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https://doi.org/10.5281/zenodo.18145466

Abstract

Pharmacovigilance (PV) is the science dedicated to detecting, assessing, understanding, and preventing adverse effects or any other drug-related problems to ensure medication safety and protect public health. It gained prominence after incidents like the thalidomide tragedy, which emphasized the need for systematic monitoring of adverse drug reactions (ADRs). PV primarily focuses on post-marketing surveillance to identify unrecognized side effects, evaluate real-world drug performance, and reduce drug-related morbidity and mortality. Historically, its development was marked by key milestones such as the Vaccine Act (1813), the Pure Food and Drug Act (1906), and the establishment of the WHO Programme for International Drug Monitoring in 1968. In India, pharmacovigilance evolved through initiatives like the National Pharmacovigilance Programme and the Pharmacovigilance Programme of India (PvPI) launched in 2010. The history of pharmacovigilance in India began with a proposal for a formal system in 1986, but it wasn't until 1998 that India joined the WHO program, though this was unsuccessful. A more successful National Pharmacovigilance Programme was launched in 2005, and it was later renamed the Pharmacovigilance Programme of India (PvPI) in 2010, with the Indian Pharmacopoeia Commission as its National Coordinating Centre. The program has since expanded to include a large network of Adverse Drug Reaction Monitoring Centers and has been recognized by the WHO.

Keywords:

Pharmacovigilance, assessment, centralizing, healthcare, communication.

1. Introduction:

The WHO defines PV as "the pharmacological science relating to the detection, assessment, understanding, and prevention of ADRs, particularly long-term and short-term ADRs of medicines." PV

performs a variety of functions, including the identification, quantification, and documentation of drug-related problems that contribute to drug-related injuries.

- **1986:** A formal adverse drug reaction (ADR) monitoring system with 12 regional centers was proposed.
- **1998:** India joined the WHO Program for International Drug Monitoring in Uppsala, Sweden, but this initial effort was not successful.
- **January 1, 2005:** The National Pharmacovigilance Programme of India (PvPI) was launched, a WHO-sponsored and World Bank-funded initiative. The Central Drugs Standard Control Organization (CDSCO) in New Delhi monitored the program through a National Pharmacovigilance Advisory Committee.
- **2010:** The program was renamed the Pharmacovigilance Programme of India (PvPI) and was officially established by the Ministry of Health. All India Institute of Medical Sciences (AIIMS), New Delhi served as the initial National Coordination Centre.
- **April 15, 2011:** The National Coordinating Centre was moved to the Indian Pharmacopoeia Commission (IPC) in Ghaziabad.
- **2015:** The WHO launched VigiAccess, a web application for accessing information on medicinal product adverse effects.
- **Present:** The PvPI has established hundreds of centers across India, trains healthcare professionals, and contributes data to the global VigiBase. It works with the CDSCO to safeguard public health by identifying and mitigating drug risks

The International Drug Monitoring program (IDM) is coordinated by the UMC in Uppsala, Sweden. There are currently 33 associate members and 104 official members worldwide, representing industrialized, developing, and impoverished nations with more than one billion potential drug users, India is the second most populous country in the world. Despite being a part of the UMC program, India makes a comparatively minor contribution to this database. The main causes of this issue are the lack of a strong ADR monitoring system and the ignorance of reporting principles among Indian medical personnel. In order to guarantee the greatest possible benefits for public health and safety, it is crucial that the medical community concentrate on the significance of ADRs. ADRs are regarded as one of the main causes of morbidity and mortality in India. ADRs are thought to be the cause of 8% of hospital admissions, and 8–19% of hospitalized patients have a significant ADR. Due to the limitations of pre-approval clinical trials, the whole adverse events profile of a new medicine may not be known when the FDA approves it for sale. Since clinical trials for new medications are typically long-term and involve populations of up to 5000, the most frequent dose-related adverse drug reactions (ADRs) are typically identified during the premarketing phase, whereas rare and long-term ADRs (Honig, 2013; Kalaiselvan

et al., 2016a; Nimesh & Ashwlayan, 2018; Organization, 2002; Schulz & Grimes, 2002; K. N. M. Singh & Kanase, 2017a, 2017b; Waller & Harrison-Woolrych, 2017).

2. Commonly used term in drug safety:

Adverse event (AE):

An adverse event (AE) is any unfavourable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (Marwitz et al., 2020).

Serious adverse event (SAE):

Serious adverse events (SAEs) are defined in drug development as any undesirable medical event that occurs during a human drug study at any dosage.

- leads to death
- is life-threatening
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- May have caused a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage (FDA & Administration, 2020).

Unexpected adverse drug reaction (UADR):

An Unexpected Adverse Drug Reaction (UADR) is an adverse reaction that:

- Is not listed in the product's labelling (e.g., package insert, summary of product characteristics)
- Is not consistent with the product's known pharmacology and toxicology profile
- Has a frequency or severity that is significantly greater than expected (ICH, 1994)

Causality assessment:

The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according established algorithms.

Cem Flow:

Software developed by UMC for collection and analysis of data in Cohort Event Monitoring.

Dechallenge:

Dechallenge refers to withdrawal of a drug from a patient the point at which the continuity, reduction or disappearance of adverse effects may be observed.

Rechallenge:

Rechallenge means the point at which a drug is again given to a patient after its previous Withdrawal.

Signals:

A Signal Term, in pharmacovigilance, refers to information that suggests a potential safety issue or hazard associated with a medicinal product, which warrants further investigation (Sultana et al., 2019).

Types of Signals:

1. Quantitative signals (e.g., statistical analysis)
2. Qualitative signals (e.g., clinical judgment)
3. Literature-based signals
4. Spontaneous report-based signal

3. History, scope and development of pharmacovigilance:

History of Pharmacovigilance (PV)

Medicinal products have long been known to have both positive and negative effects. More recently, significant adverse reactions linked to medical products have led to the development of regulatory modifications and an effort to identify drug safety problems as soon as feasible. Sponsors and regulatory agencies utilize pharmacovigilance to quickly identify adverse effects linked to medical products. Numerous drug-related catastrophes throughout history have led to the creation of numerous legislations. The following is a description of the numerous drug related disasters and regulatory actions:

- **Vaccine Act:** The United States 12th Congress passed the Vaccine Act of 1813 in an effort to promote smallpox immunization. It was enacted on February 27, 1813, and it was revoked on May4, 1822. The first federal law pertaining to pharmaceutical consumer protection was thisAct.
- **Biological Control Act** (**BCA**): The United States of America (US) approved the Biological Control Act in 1902 as a result of vaccine-related deaths of children. Additionally, the United States passed the Pure Food and Drug Act in 1906 to prohibit the production, distribution, or transportation of tainted, mislabelled, toxic, or harmful foods, medications, and liquids, as well as to control traffic in and out of the country.

This law addressed certain issues of drug safety, but not their effectiveness

- **Thalidomide Tragedy and Regulatory Action**

Thalidomide was first released in 1957 as a safe and effective sedative, and it was later discovered to be beneficial in treating morning sickness. It was thought to be so safe that it was sold over the counter in

several nations. However, it was phased out of much of the pharmaceutical industry beginning in late November 1961. This was because it was discovered to be the cause of an epidemic of at least 10,000, maybe 100,000, infants born with severe birth defects to mothers who used thalidomide during pregnancy (Johnson et al., 2018; Magazanik, 2015; Smithells & Newman, 1992; Stephens & Brynner, 2009; Vargesson, 2019). The archetypal image of a thalidomide survivor is a person with phocomelia of the arms, where the long bones of the arm are absent or shortened, and the digits articulate with the shoulder or at the end of a shortened humerus. and ulna. However, thalidomide has an impact on a wide range of tissues, including the legs, eyes, ears, face, cardiovascular system, gastrointestinal system, reproductive system, urinary system, and spine (Smithells & Newman, 1992).

Unfortunately, it has been estimated that up to 40% of babies die in their first year of life due to internal organ developmental variations such as bowel atresia and heart problems (Smithells & Newman, 1992; Vargesson, 2019). It is also clear that no two thalidomide survivors are identical, highlighting the widespread harm this drug can inflict, most likely related to the period of exposure and genetic background, which differs between pregnant women (Vargesson, 2019),(Stephens & Brynner, 2009). The discontinuation of thalidomide has resulted in significant global changes in drug and medicine testing (Kelsey, 1988)(Vargesson, 2013).

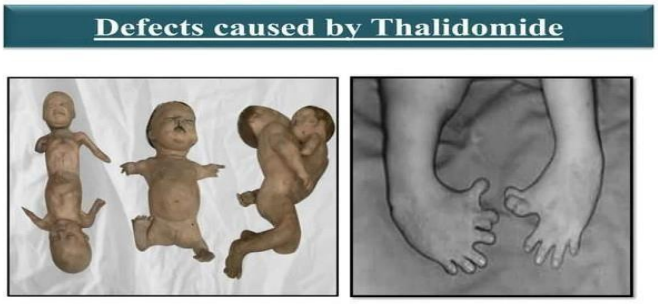


Figure. 2: Defects caused by thalidomide

The sequential Pharmacovigilance developments (Agrawal et al., 2022a, 2022b; Ghosh et al., 2012; Jadhav & Chakraborthy, 2011; Kulkarni et al., 2013; Shuka et al., 2012).

3.1. Scope of Pharmacovigilance:

PV has evolved significantly since the WHO technical report in 1972, and it continues to be a vibrant clinical and scientific profession. To address the risks associated with pharmaceutical and biological therapies, including vaccinations, it's crucial to address the growing diversity and potency of available options. The risk of harm is reduced when medicines are used by an informed health professional and patients who understand and accept responsibility for their medications. When side effects and toxicity are discovered, especially when they were previously unknown in relation with the medicine, it is critical that they are analysed and efficiently presented to an audience with the ability to interpret the data. This is the role of PV. Much progress has been made in this regard. However, additional work is needed to integrate the field into clinical practice and public policy settings. A pharmaceutical business in India

must fundamentally take out operations such as collection and expedited reporting of major unexpected ADRs in order to meet the PV responsibilities for its marketed products as per rules (Suke et al., 2015a). illustrates a typical structure for PV studies, which includes persons working at various levels, organizational units and their functions.

Development of Pharmacovigilance

Year	Developments
1747	**The very first known clinical trials by James Lind proved the usefulness of lemon juice in preventing scurvy.**
1937	**Death of more than 100 children due to toxicity of sulphanilamide.**
1950	**Aplastic anaemia was reported due to Chloramphenicol toxicity.**
1961	**Worldwide tragedy due to thalidomide toxicity.**
1963	**16th World Health congregation recognizes significant to rapid action on Adverse Drug Reactions (ADRs).**
1968	**WHO research project for international drug monitoring on a pilot scale.**
1996	**Global standards level clinical trials initiated in India.**
1997	**India attached with WHO Adverse Drug Reaction Monitoring Program.**
1998	**Initiation of Pharmacovigilance in India**
2002	**67th National Pharmacovigilance Centre established in India.**
2004-05	**India launched National Pharmacovigilance Program.**
2005	**The accomplishment of structured clinical trials in India**
2009-10	**Pharmacovigilance Program (PvPI) started.**

Table.1 Development of pharmacovigilance history

4. Future perspective of pharmacovgilance in india:

The future of pharmacovigilance in India looks promising, driven by technological advancements, regulatory enhancements, and growing awareness among healthcare professionals. As India continues to strengthen its pharmacovigilance framework, several key trends and developments are expected to shape the landscape. (Kalaiselvan et al., 2019)

5. Digital transformation and technological integration:

Artificial Intelligence (AI) and Machine Learning (ML): AI and ML will play a pivotal role in improving signal detection, data mining, and pattern recognition in pharmacovigilance databases. These technologies will enable faster and more accurate identification of adverse drug reactions (ADRs), enhancing regulatory decision-making.

Digital Reporting Systems: The adoption of electronic reporting systems, such as ViGiFlow, and mobile applications for ADR reporting will streamline data collection and improve reporting efficiency. This digital shift will help bridge gaps in traditional pharmacovigilance practices.

Blockchain Technology: While not yet widely implemented, blockchain has the potential to enhance data integrity and traceability in pharmacovigilance, ensuring secure and transparent reporting

6. Strengthening regulatory framework:

India's regulatory agencies, including the Central Drugs Standard Control Organization (CDSCO), are expected to enforce stricter pharmacovigilance guidelines, aligning with global standards (ICH E2E guidelines).

Periodic Safety Update Reports (PSURs) will become more robust, with enhanced risk management plans and benefit-risk assessments for marketed drugs.(Subbaiah et al., 2022)

7. Enhanced stakeholder engagement:

Healthcare Professional Training: Continuous education and training programs will be critical to address underreporting of ADRs. Initiatives like the Indian Pharmacopoeia Commission's (IPC) Skill Development Programmes will foster a culture of proactive pharmacovigilance.

Patient-Centric Approach: Greater involvement of patients in reporting ADRs and providing real-world evidence will improve drug safety monitoring.

8. Collabration and global harmonization:

India will strengthen collaborations with global health authorities (WHO, EMA, US FDA) to harmonize pharmacovigilance practices and leverage international expertise.

The IPC's recognition as a WHO Collaborating Centre for Medicines and Vaccine Safety underscores India's growing role in global pharmacovigilance efforts.

9. Focus on emerging challenges:

Personalized Medicine: Pharmacovigilance will increasingly incorporate genetic data to predict drug responses and tailor safety monitoring.

Real-World Evidence (RWE): Analysis of electronic health records (EHRs) and prescription data will provide deeper insights into drug safety in diverse populations.

Public Health Emergencies: Lessons from COVID-19 will drive the integration of pharmacovigilance into emergency response plans, ensuring rapid ADR tracking during crises.(Janarthanan et al., 2025)

10. Addressing persistent challenges:

Underreporting: Despite progress, underreporting remains a key challenge. Digital tools and awareness campaigns will be critical to improving reporting rates.

Rural-Urban Disparities: Expanding pharmacovigilance networks to rural areas and leveraging community health workers will be essential for comprehensive coverage.

11. Indian regulatory bodies:

11.1. Committees Responsible for Adverse Drug Monitoring:

In India, multiple committees have been set up to check over side effects of drugs and ensuring pharmacovigilance operates smoothly within each committee. These organizations are vital for supervising and regulating the possible concerns with medications, playing a key part in making sure pharmacovigilance efforts operate successfully (Chopra & Desai, 2013). These committees encompass a range of institutions, starting from the Adverse Drug Reaction Monitoring Centres (AMCs) and include the Uppsala Monitoring Centre (UMC), ensuring a systematic and coordinated approach to supervising drug safety (Kalaiselvan et al., 2016b).

11.2. National Coordination Centre (NCC) for PvPI:

In the National Pharmacovigilance Programme of India, the NCC plays a crucial part to collecting, evaluating and distributing information on ADRs reported all across the nation. It has some key function to run smoothly such as data Collection, data processing and analysis. Where AMCs are sent the data online from all across the India to NCC. The reports contain specifics of patient information, particular medicine details and suspected ADRs and verify the data, go ahead is belongs to NCC staffs. They should examine the data with respect to identify trends; safety alerts and the data should demand additional investigation. The NCC is also responsible for disseminating the critical information to stakeholders, who are regulatory authorities to debate regulatory ultimate decision on drug safety. The healthcare practitioner should convey information about probable adverse medication responses. Publication should be priorities of reports on ADR trend in India. The NCC lies under Indian Pharmacopoeia Commission in Ghaziabad, Uttar Pradesh. Personal working in NCC are well qualified specialists with expertise in pharmacovigilance, pharmaceuticals and data analysis (Rukmangathen et al., 2017).

11.3. CDSCO in adverse drug reaction monitoring:

The clearance of different medical equipment, pharmaceuticals and cosmetics in India is carried out by CDSCO. For monitoring of adverse drug reactions in pharmaceutical industry the relevant working body is CDSCO. The collecting of data pertaining to safety and efficacy of medications and evaluation carried out based on reported ADRs (Godiyal, 2019). For the pharmaceutical business it is required to report adverse medication response to CDSCO, further the information provides to healthcare practitioners. By the exchange of information helps to create the strategies to decrease the risk associated to adverse medication response and will boost the safety. CDSCO's major aim is to enhance PvPI, which is lead to safeguard public health. NCC at the IPC performs the pharmacovigilance operations under PvPI, which is beneficial for novel drug-related safety concerns and safety monitoring of marketed medications. The function in pharmacovigilance or in monitoring the adverse drug responses cannot be overlooked, as it validates that pharmaceuticals are safe for patients to use, safeguard public health and improves patient health in a positive manner. However, the reporting to CDSCO by pharmaceutical firms is crucial to strengthen pharmacovigilance programs (A. Singh & Bhatt, 2012).

11.4. Medical Council of India (MCI) in pharmacovigilance:

MCI is coordinated with PvPI. This cooperation influences awareness of PvPI among the stakeholders. Recent facts are influencing the improvement of relation between these two government entities. Hence, it is increasing the adverse medication reaction reporting and monitoring in India. The influence of the collaboration is obvious via the results of educational programs and workshops. This helps to conscious healthcare workers to play a key part in adverse drug monitoring in patient safety. This collaboration helps to concentrate and targeted strategy to integrating the medicinal and medical sectors together. The impact of the partnership is highly understanding and participating, resulting more aggressive measures

to enhance adverse medication monitoring and reporting system finally leads to progress Cing patient safety in the country. (Beedimani & Zaman, 2018).

11.5. World Health Organization Uppsala Monitoring Centre (WHO UMC):

The WHO which is responsible for International Drug Monitoring and its headquarters at Uppsala Monitoring Centre located in Sweden, plays a vital role in adverse drug reaction monitoring in India. It is a global center for gathering and analyzation of adverse drug reaction reported data from diverse countries. It gives tools and numerous resourced to India for establishing and managing the pharmacovigilance programme which is directly dealing with adverse drug reaction. It supports the reporting and tracking of adverse medication reaction in different country around the globe (Behera et al., 2018). The PvPI is structure by inspiration from WHO UMC standards and recommendations like other nations. The techniques and methods employed by PvPI is linked with WHO UMC system. The data collected by PvPI is forwarded to WHO UMC. This is allowing the WHO UMC to collect the data from all over the country and world which give a clear, verifiable and accurate data collection (Tantikul et al., 2008).

12. Conclusion:

In conclusion, the article emphasizes that pharmacovigilance is an indispensable component of healthcare systems, ensuring the safe and effective use of medicines. It highlights that despite the establishment of global and national programs, such as the Pharmacovigilance Programme of India (PvPI), there is still a need for stronger awareness, active participation, and consistent reporting of adverse drug reactions among healthcare professionals. The integration of pharmacovigilance into clinical practice, education, and regulatory frameworks is essential to enhance patient safety and minimize drug-related risks. The collaboration between national regulatory bodies like CDSCO, NCC, and international organizations such as the WHO Uppsala Monitoring Centre plays a vital role in building a robust drug safety network. Ultimately, continuous efforts to strengthen pharmacovigilance infrastructure, promote education and training, and encourage spontaneous reporting will lead to a safer and more reliable healthcare system globally.

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Citation

Mangilal, Sumit Lohia, Lovish, Amit Chawla, & Rani Payal. (2026). Pharmacovigilance: History and development in india. Scienxt Journal of Pharmaceutical Sciences, 4(1). https://doi.org/10.5281/zenodo.18145466