Adverse Drug Reactions and the Evolution of Pharmacovigilance: Comparative Insights from Global Systems and India (1848–2025)

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***Abstract*-** Background: Pharmacovigilance (PV) is the science of detecting, assessing, and preventing adverse drug reactions (ADRs), which are often not fully recognised in pre-marketing clinical trials [85].

Objective: This review analyses the historical development of PV (1848–2025), comparing global milestones with Indian initiatives, and identifies future challenges and opportunities [86].

Methods: A narrative review of sentinel ADR cases, regulatory milestones, and programme developments was undertaken, with emphasis on international systems (FDA-FAERS, EMA-EudraVigilance, WHO-VigiBase) and India's PvPI [87].

Results: Six historical eras were mapped. Era 1 (1848–1937) established the concept of ADR recognition through sentinel cases. Era 2–3 saw regulation and global collaboration following thalidomide. Era 4–5 introduced harmonisation, digitalisation, and India's entry into WHO monitoring. Era 6 demonstrated real-time PV during COVID-19, with India contributing significantly through PvPI [88]. Presently, global systems are AI-driven and transparent, while India has built a vast reporting infrastructure with inclusive patient participation [89].

Conclusion: Pharmacovigilance has evolved from isolated clinical observations into a global, technology-enabled safety network. India is now a major contributor but needs to expand community reporting, adopt AI-driven analytics, and enhance transparency to match global standards [90]. Future PV will rely on AI, big data, and deeper patient engagement to ensure universal drug safety [91].

***Index Terms*-** Pharmacovigilance, Adverse Drug Reactions, India, Global, WHO, PvPI, Drug Safety, History, Future Directions

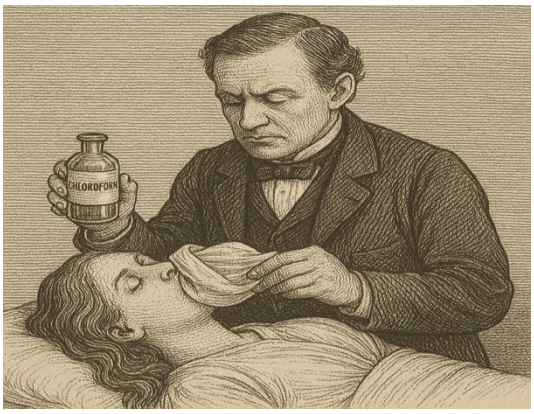
I. INTRODUCTION

This article guides a stepwise walkthrough by Experts for writing a successful journal or a research paper starting from inception of ideas till their publications. Research papers are highly recognized in scholar fraternity and form a core part of PhD curriculum. Research scholars publish their research work in leading journals to complete their grades. In addition, the published research work also provides a big weight-age to get admissions in reputed varsity. Now, here we enlist the proven steps to publish the research paper in a journal.

The safety of medicines has always been one of the most critical priorities for healthcare systems worldwide, because the same drugs that provide therapeutic benefit can also cause unexpected harm. [1] From the earliest herbal remedies used in ancient traditions to modern biotechnology-based treatments, society has consistently faced the dual reality of benefit and risk. [2] With the expansion of the pharmaceutical industry during the twentieth century, the introduction of synthetic drugs, and the widespread practice of polypharmacy, the absolute number of adverse drug reactions (ADRs) being observed increased substantially, underlining the need for structured monitoring. [3]

The science that fulfils this function is called pharmacovigilance—a term derived from the Greek word pharmakon (drug) and the Latin vigilare (to keep watch). It has been formally defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem." [4] Unlike clinical trials, which are

performed under controlled conditions with limited sample sizes, pharmacovigilance extends drug safety assessment to the real world, where factors such as genetics, environment, age, comorbidities, and interactions produce varied outcomes. [5] This makes pharmacovigilance a cornerstone of modern public health, ensuring that the benefit–risk balance of medicines remains favourable throughout their lifecycle. [6]



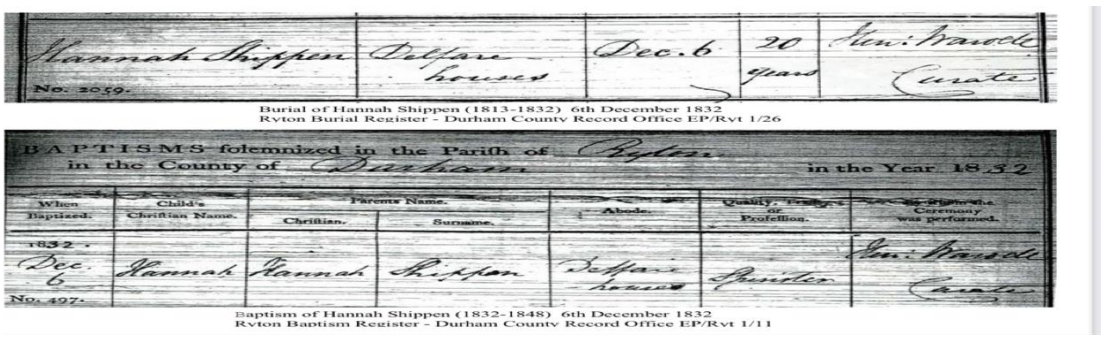
The history of pharmacovigilance has been strongly shaped by tragedies that revealed the dangers of inadequate monitoring. In the nineteenth century, fatalities from chloroform anesthesia (such as the death of Hannah Greener in 1848) demonstrated the risks of poorly controlled therapies. [7] The St. Louis diphtheria antitoxin contamination (1901) showed that biologics could transmit lethal infections when quality controls failed. [8] The Elixir Sulfanilamide disaster (1937) in the United States resulted in more than 100 deaths from diethylene glycol poisoning, forcing new legal frameworks. [9] Later, the thalidomide catastrophe (1961)—first highlighted by Dr. William McBride in Australia and Dr. Widukind Lenz in Germany—caused thousands of birth defects worldwide and led directly to the establishment of international monitoring systems. [10]

These episodes served as turning points, each pushing governments to strengthen regulatory frameworks. They also motivated the creation of global and national pharmacovigilance networks. The US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the WHO Uppsala Monitoring Centre (UMC) developed frameworks for structured adverse-event reporting and signal detection. [11] In India, although progress was initially slower under colonial administration, important developments later followed with the Drugs and Cosmetics Act (1940), the creation of the Central Drugs Standard Control Organization (CDSCO), and finally the establishment of the Pharmacovigilance Programme of India (PvPI), which has now grown into one of the largest national PV networks worldwide. [12]

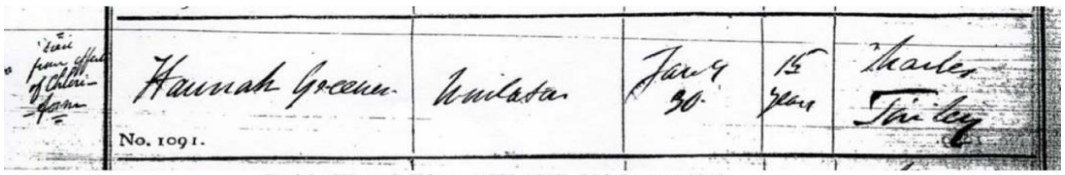
> Era 1 (1848–1937) — Foundations, Signals, and the Pre-Regulatory World

♦ Global

The sentinel case that set the tone (1848).
On 29 January 1848, 15-year-old Hannah Greener died after chloroform anaesthesia for a toenail procedure—widely regarded as the first prominently recognized ADR in



medical literature. Dr. James Young Simpson documented the fatality in The Lancet, establishing a contemporaneous medical record of an unexpected drug-related death.



Burial of Hannah Shippen(1832-1848) 30th January 1848
Winlaton Register of Burials - Durham County Record Office EP/Win 1/21

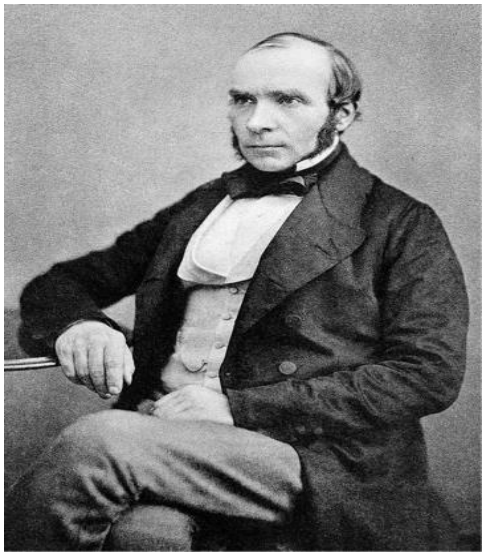
[11] Soon after, Dr. John Snow investigated and published analytic remarks in The Lancet, arguing that poorly controlled chloroform exposure with cardiopulmonary depression likely precipitated the event—one of the earliest examples of a named clinician proposing a pathophysiological mechanism for a sentinel case. [12]

Why this matters methodologically: the Greener episode crystallized a pattern that would later define pharmacovigilance culture—a specific reporter, a peer-read publication, and a reasoned causality argument—even though no formal reporting system existed in 1848. [4]

How risks were "seen" before systems existed.

Through the late 19th and early 20th centuries, harms from therapeutics such as digitalis (arrhythmias), opiates (respiratory depression), arsenicals (neuropathy/dermatitis), and anaesthetics appeared as isolated case notes or small series by clinicians and hospital departments. [3,13] These reports circulated in journals and society proceedings, teaching bedside recognition of unusual patterns, yet they lacked national pooling, standard terminology, or denominator data—so signals were slow to form and easy to dismiss as coincidences. [3,4]

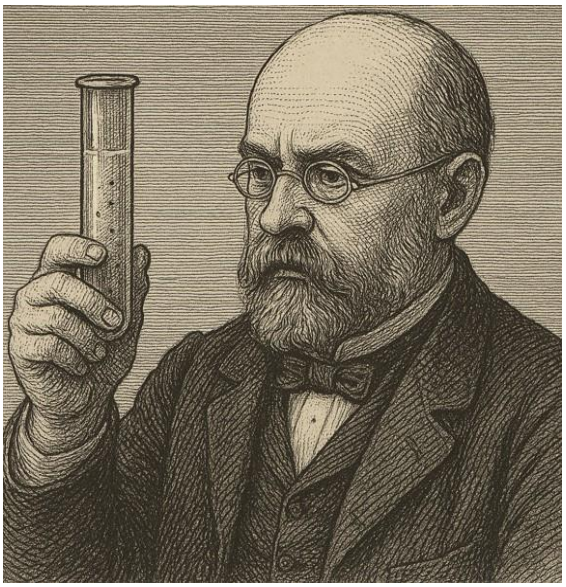
At the same time, synthetic pharmaceuticals were proliferating, and premarket safety testing (toxicology/clinical) remained limited, with regulatory expectations still evolving—conditions that increased the chance of unforeseen toxicities reaching patients. [5,8]



When biologics turned deadly (1901).

The St. Louis diphtheria antitoxin disaster (1901) involved tetanus-contaminated horse serum, killing multiple children and proving that even life-saving biologics can transmit lethal pathogens if quality systems fail. [14] Dr. William H. Park traced and documented the contamination in public-health bulletins exemplifying early official outbreak investigation and transparent reporting.

[15] The scandal catalyzed the Biologics Control Act (1902)—the first statute anywhere to regulate manufacture, purity, and safety of biologic preparations, laying a legal template for later drug-safety laws. [16]



The catastrophe that forced small-molecule regulation (1937).
The Elixir Sulfanilamide crisis unfolded when a manufacturer dissolved sulfanilamide in diethylene glycol (DEG) to make a palatable liquid; the solvent is nephrotoxic, and more than a hundred deaths followed in the US. [17] A key early alarm came from Dr.
A. S. Calhoun (letter dated 22 Oct 1937), explicitly naming fatalities and implicating the new elixir—an identifiable "first reporter" in the written record. [18] The US FDA conducted a nationwide field investigation, retrieving bottles, reconstructing clinical courses, and confirming DEG toxicity as the proximate cause—an inquiry that read like an early, large-scale signal validation exercise. [18] In direct response, Congress enacted the Federal Food, Drug, and Cosmetic Act (1938), which mandated pre-market safety and expanded federal inspection and enforcement powers—effectively inaugurating modern statutory drug-safety regulation for small molecules. [19]

> **What Era 1 proves (global take-aways).**

1. Named clinicians + journals can detect harms even without formal systems, but diffusion is slow and preventability is limited. [3,4]
2. Legal authority—first for biologics (1902), later for all drugs (1938)—was necessary to transform sporadic warnings into reliable public-health protection. [16,19]

♦ **India**

Position in the pre-independence landscape.
During this entire era, India had no structured pharmacovigilance system. Drug supply chains and regulatory levers were embedded in colonial administration, with most finished medicines imported and little local capacity to test, codify, or centrally collate adverse outcomes. [20]

Documentation existed—but was fragmented.
Adverse effects were occasionally described in Indian medical journals and hospital notes (e.g., quinine intolerance, opiate-related events), often authored by clinicians in medical colleges; however, these remained local clinical observations with no national pooling, no standardized case forms, and no official trigger for regulatory action. [20] Regulatory base still forming.
By the end of Era 1, India lagged Western jurisdictions that had already been galvanized by the antitoxin and sulfanilamide disasters into binding federal statutes; India's comprehensive drug law and rules would come only in the next era (1940/1945), initially emphasizing quality and control of manufacture/import rather than post-marketing safety surveillance. [13,20]

Micro-summary (why this era matters to your review)

a. It establishes who first reported key sentinel harms (Greener's surgeon/Snow; Calhoun in 1937) and who documented/verified them officially (Park; FDA), linking named reporters to systemic responses. [11–12,15,18]
b. It shows how law follows tragedy: biologics (1902) and small molecules (1938), creating the legal scaffolding upon which formal pharmacovigilance would later be built. [16,19]
c. It locates India's starting point: clinical awareness but no national mechanism, setting up the need for later Indian reforms. [20]

> **Era 2 (1938–1960): Early Regulation and Case-Series Culture (Corrected)**

♦ **Global Developments**

The Elixir Sulfanilamide disaster (1937) led to the US Food, Drug, and Cosmetic Act
(1938). The first alarm was raised by Dr. A. S. Calhoun, who in his letter dated 22 October 1937 described deaths and linked them to the new sulfanilamide preparation, making him the first physician to report the crisis in writing [13]. The US FDA investigators subsequently confirmed the solvent diethylene glycol as the cause of fatalities and officially documented the case in federal bulletins [14]. This sequence established an early model of clinician detection followed by regulatory confirmation.

In the 1940s, penicillin allergy emerged as a notable ADR. It was first observed by physicians in military hospitals during World War II, when patients developed urticaria, anaphylaxis, and serum sickness-like reactions. The first published accounts appeared in The Lancet (1942) and JAMA (1944), formally identifying penicillin hypersensitivity as an ADR [15].

Streptomycin-related ototoxicity was first noticed by Dr. H. Waksman's research group (1944–46) during early trials, but it was clinicians at TB sanatoria who documented cases of irreversible hearing loss. These were published in early case series in US and European journals, which established streptomycin ototoxicity as a dose- and duration-related ADR [16].

Chloramphenicol-induced aplastic anemia was first noticed in 1950 by clinicians in the United States who treated patients with prolonged therapy. The ADR was formally published in 1952 in the journal Blood, where the first fatal cases of aplastic anemia

attributed to chloramphenicol were described [17]. This case showed the unique ability of clinicians to "connect the dots" across rare events and raise alarms through publication.

Thus, in this era, most ADRs were first found by practicing clinicians and reported/published in leading journals. While structured PV systems were absent, these reports collectively shaped drug regulation and pharmacology teaching.

♦ **Indian Developments**

In India, this era saw the foundation of drug regulation through the Drugs and Cosmetics Act (1940) and Rules (1945), passed under colonial administration to ensure drug quality and import control [18]. However, pharmacovigilance in the modern sense had not yet begun.

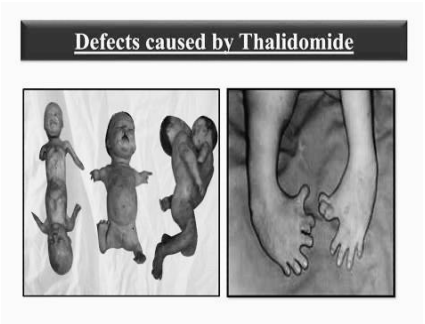
Adverse events were occasionally noted by Indian clinicians. For instance, cases of quinine hypersensitivity, sulfa drug rashes, and opium dependence were observed in hospitals and published in Indian medical journals [19]. These were typically individual clinicians who noticed reactions and wrote reports, but no central authority compiled or validated them [20].

Thus, while Western countries were documenting ADRs in journals like The Lancet, JAMA, and Blood, India's reporting remained local and academic, with no structured pharmacovigilance programme in place until later decades. [21]

♦ **Era 3 (1961–1985): Thalidomide Tragedy and the Birth of International Monitoring**

> **Global Developments**

The thalidomide catastrophe (1961) marked a turning point in drug safety history. Thalidomide, introduced in the late 1950s as a sedative and treatment for morning sickness, was first suspected by clinicians and parents who observed an unusual rise in infants born with limb deformities. Dr. William McBride, an Australian obstetrician, formally reported the association in a short communication to The Lancet (1961), making him the first to publish a warning in medical literature [26]. Around the same time, Dr. Widukind Lenz, a German pediatrician, conducted systematic clinical investigations and publicly confirmed the causal link in late 1961, presenting his findings at a medical conference and later in scientific publications [27]. Together, McBride's initial alert and Lenz's confirmatory epidemiological work created a global recognition of teratogenic risk.



The immediate consequence was the withdrawal of thalidomide from markets across Europe, Australia, and other countries by 1962. The incident demonstrated how the absence of rigorous pre-market teratogenic testing could lead to worldwide human tragedy. In the United States, the drug never gained approval, largely because Dr. Frances Kelsey, a medical officer at the US FDA, resisted company pressure and withheld licensing, citing inadequate safety data. Her stance became an early model of regulatory vigilance [28].

In response to thalidomide, the US Congress passed the Kefauver–Harris Amendments (1962) to the FD&C Act, which made proof of efficacy and safety mandatory before drug approval and strengthened requirements for informed consent and adverse reaction reporting [29]. In the United Kingdom, the government introduced the Yellow Card Scheme (1964), which allowed physicians to voluntarily submit reports of suspected ADRs to a national authority, institutionalising spontaneous reporting for the first time [30]. At the global level, the World Health Organization launched the International Drug Monitoring Programme in 1968, designed to collect and analyse Individual Case Safety Reports (ICSRs) from participating countries [31]. The programme was later anchored at the Uppsala Monitoring Centre (UMC), Sweden, which created and maintained VigiBase, now the world's largest ADR database [32].

Thus, this era shifted pharmacovigilance from isolated clinician reports to the beginning of formal, national, and international monitoring frameworks, with thalidomide as the defining catalyst.

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> **Indian Developments**

In India, this period was still marked by the absence of a formal pharmacovigilance programme. ADRs continued to be reported only in scattered fashion by clinicians in teaching hospitals and published in journals, often describing toxicities such as quinine reactions, sulfonamide rashes, and antimonial toxicity [33]. However, these remained individual academic contributions, with no national system to collect or act upon these reports.

Importantly, while India observed global regulatory changes, such as the Kefauver–Harris Amendments in the US and the WHO programme, the country did not yet join the international monitoring system. The regulatory structure was focused primarily on drug quality and licensing under the Drugs and Cosmetics Act, and ADR reporting remained voluntary and fragmented [34].

By the end of this era, global pharmacovigilance had begun to take shape, but India remained in a pre-programme stage, relying on individual clinicians rather than a coordinated infrastructure.

♦ **Era 4 (1986–2000): Harmonisation and India's First Steps into Pharmacovigilance**

> **Global Developments**

By the mid-1980s, drug safety had matured from scattered case reports and national programmes into a global policy priority. Regulatory agencies in the United States, Europe, and Japan recognised that differences in safety reporting requirements created barriers for international companies and slowed the identification of global signals [35].

To address this, the International Conference on Harmonisation (ICH) was launched in 1990, bringing together regulators and industry from the US, EU, and Japan. ICH issued harmonised guidelines on expedited safety reporting, Periodic Safety Update Reports (PSURs), and signal evaluation frameworks, allowing data to be exchanged across borders in a uniform format [36]. This was a decisive step toward a truly global pharmacovigilance language.

In Europe, the establishment of the European Medicines Agency (EMA, 1995) created a centralised structure for evaluating and monitoring drug safety across EU member states. The EMA initiated centralised databases and legal requirements for marketing authorisation holders to submit safety reports electronically, laying the foundation for EudraVigilance [37].

In the United States, the FDA launched MedWatch in 1993, a nationwide safety information and adverse event reporting programme. For the first time, clinicians and patients had a unified reporting channel that fed directly into federal review systems, greatly improving case volume and quality [38].

This era also saw the strengthening of signal detection methodologies—from narrative case aggregation to computer-assisted databases—representing a transition from manual review to early digital tools.

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> **Indian Developments**

In India, this period marked the very first official steps toward pharmacovigilance. In 1986, during the Seventh Five-Year Plan, the government launched the Adverse Drug Reaction Monitoring Scheme at select tertiary institutions such as KEM Hospital (Mumbai), AIIMS (New Delhi), and JIPMER (Puducherry) [39]. These centres were tasked with documenting ADRs and sending reports to a central unit.

However, due to limited funding, lack of trained manpower, and poor awareness among clinicians, the programme struggled to generate momentum. Reporting was inconsistent, and awareness outside tertiary hospitals remained negligible [40].

A critical milestone came in 1997, when India officially joined the WHO Programme for International Drug Monitoring (PIDM). This allowed Indian Individual Case Safety Reports (ICSRs) to be uploaded into VigiBase, the global ADR database maintained at the Uppsala Monitoring Centre [41]. Although the number of cases contributed at first was modest, this marked the formal entry of India into global pharmacovigilance collaboration.

By the year 2000, while Western countries had developed harmonised, electronic, and centralised PV infrastructures, India was still in an early pilot stage. Yet, the foundations had been laid: a small national scheme, WHO membership, and early attempts to train clinicians in ADR reporting. These seeds would soon develop into a structured national programme in the following decade.

♦ **Era 5 (2001–2012): Digitalisation and the Pharmacovigilance Programme of India (PvPI) Launch**

> **Global Developments**

The early 2000s marked a revolution in pharmacovigilance with the digitalisation of safety databases. In Europe, EudraVigilance officially became operational in 2001, providing a centralised electronic system for Individual Case Safety Reports (ICSRs) across EU member states. This was one of the first large-scale digital repositories designed for real-time safety data submission and analysis [42].

In the United States, the FDA consolidated its systems into the FDA Adverse Event Reporting System (FAERS) in 2002. For the first time, all post-marketing safety data—voluntary MedWatch submissions, mandatory manufacturer reports, and clinical trial safety updates—were integrated into a single electronic platform [43]. This allowed faster signal detection and greater transparency.

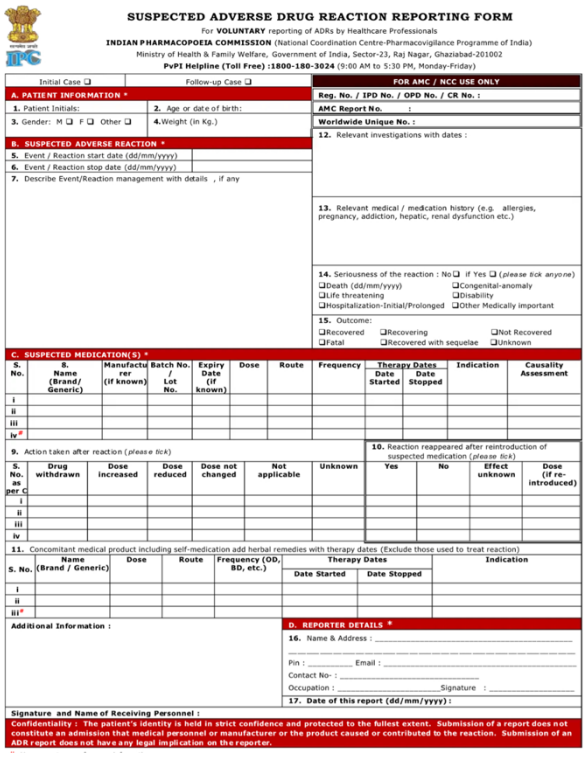
A defining moment of this era was the Vioxx (rofecoxib) withdrawal in 2004.
Cardiovascular risks were first noted during the VIGOR clinical trial (2000) by Dr. Claire Bombardier and colleagues, who published their findings in the New England Journal of Medicine. This was the first formal signalin the scientific literature, showing increased risk of myocardial infarction in rofecoxib users [44].
Subsequent post-marketing case reports and FDA reviews confirmed the association, leading to the global withdrawal of Vioxx in September 2004 [45]. The case highlighted the critical role of clinician reporting + academic publication + regulatory investigation in protecting patients.

Another milestone was the European Union Pharmacovigilance Legislation of 2010 (effective 2012), which represented the most comprehensive reform of EU drug safety law. It established the Pharmacovigilance Risk Assessment Committee (PRAC), introduced direct patient reporting, and strengthened the requirements for Risk Management Plans (RMPs) and Periodic Safety Update Reports (PSURs) [46]. This legislation formalised patient participation in PV and made proactive risk minimisation mandatory.

By the end of this era, pharmacovigilance had transitioned into the digital age, with electronic databases, stronger legal frameworks, and clear global examples of how safety signals could directly influence regulatory action.

> **Indian Developments**

For India, this era was transformative. After earlier fragmented attempts in the 1980s and 1990s, the government formally launched the Pharmacovigilance Programme of India (PvPI) in 2010 [47]. Initially coordinated by the National Coordinating Centre
(NCC) at AIIMS, New Delhi, the programme aimed to systematically capture ADRs across the country. In 2011, the NCC was shifted to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, giving PvPI a permanent institutional base [48].



SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For **VOLUNTARY** reporting of ADRs by Healthcare Professionals
INDIAN PHARMACOPOEIA COMMISSION (National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India, Sector-23, Raj Nagar, Ghaziabad-201002
PvPI Helpline (Toll Free) :1800-180-3024 (9:00 AM to 5:30 PM, Monday-Friday)

Initial Case ❑ Follow-up Case ❑

A. PATIENT INFORMATION *

1. Patient Initials:
2. Age or date of birth:
3. Gender: M ❑ F ❑ Other ❑
4. Weight (in Kg.)

B. SUSPECTED ADVERSE REACTION *

5. Event / Reaction start date (dd/mm/yyyy)
6. Event / Reaction stop date (dd/mm/yyyy)
7. Describe Event/Reaction management with details , if any

FOR AMC / NCC USE ONLY

Reg. No. / IPD No. / OPD No. / CR No. :
AMC Report No. :
Worldwide Unique No. :

12. Relevant investigations with dates :
13. Relevant medical / medication history (e.g. allergies, pregnancy, addiction, hepatic, renal dysfunction etc.)
14. Seriousness of the reaction : No ❑ If Yes ❑ (*please tick anyone*)
❑Death (dd/mm/yyyy) ❑Congenital-anomaly
❑Life threatening ❑Disability
❑Hospitalization-Initial/Prolonged ❑Other Medically important
15. Outcome:
❑Recovered ❑Recovering ❑Not Recovered
❑Fatal ❑Recovered with sequelae ❑Unknown

C. SUSPECTED MEDICATION(S) *

S. No.	8. Name (Brand/ Generic)	Manufacturer (if known)	Batch No. / Lot No.	Expiry Date (if known)	Dose	Route	Frequency	Therapy Dates: Date Started	Therapy Dates: Date Stopped	Indication	Causality Assessment
i											
ii											
iii											
iv#											

9. Action taken after reaction (*please tick*)

S. No. as per C	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown
i						
ii						
iii						
iv						

10. Reaction reappeared after reintroduction of suspected medication (*please tick*)

Yes	No	Effect unknown	Dose (if re-introduced)

11. Concomitant medical product including self-medication add herbal remedies with therapy dates (Exclude those used to treat reaction)

S. No.	Name (Brand / Generic)	Dose	Route	Frequency (OD, BD, etc.)	Therapy Dates: Date Started	Therapy Dates: Date Stopped	Indication
i							
ii							
iii#							

Additional Information :

D. REPORTER DETAILS *

16. Name & Address :
Pin : Email :
Contact No- :
Occupation : Signature :
17. Date of this report (dd/mm/yyyy) :

Signature and Name of Receiving Personnel :

Confidentiality : The patient's identity is held in strict confidence and protected to the fullest extent. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction. Submission of an ADR report does not have any legal implication on the reporter.

By 2012, India had established around 60 Adverse Drug Reaction Monitoring Centres (AMCs), linked via the WHO-supported VigiFlow software, enabling real-time electronic submission of reports into VigiBase [49]. This integration ensured that Indian data directly contributed to global signal detection for the first time on a routine basis.

During this time, India also began strengthening regulatory frameworks for PV. The Central Drugs Standard Control Organization (CDSCO) mandated that Marketing Authorisation Holders (MAHs) maintain pharmacovigilance systems and report serious adverse events. Training workshops for healthcare professionals and pharmacology residents were also initiated to improve awareness and reporting culture [50].

Thus, by the end of 2012, India had transitioned from scattered case reports to a structured, internationally integrated pharmacovigilance programme. This development aligned India with global PV practices and laid the groundwork for the massive expansion of PvPI in the next decade.

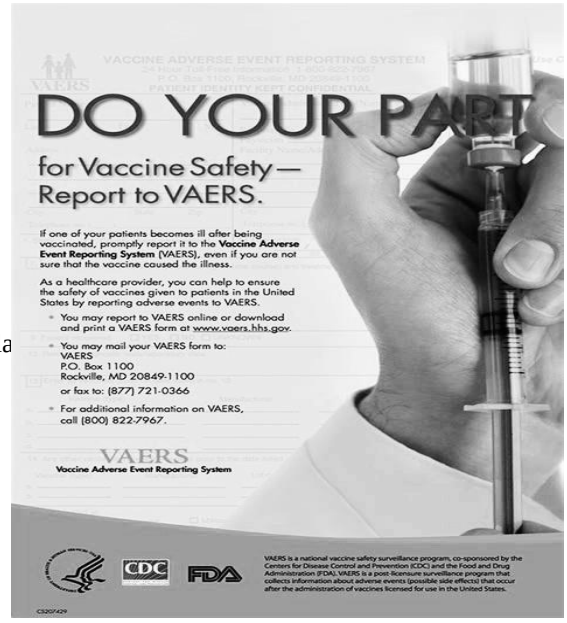
♦ Era 6 (2013–2025): Real-time Pharmacovigilance, Artificial Intelligence, and the COVID-19 Stress Test

> Global Developments

The last decade has been marked by the digital transformation of pharmacovigilance. In 2017, the FDA launched the FAERS Public Dashboard, providing real-time, publicly accessible data from its Adverse Event Reporting System. For the first time,

clinicians, researchers, and even patients could directly query the database to identify ADR patterns, improving transparency and accountability [51].

That same year, the European Medicines Agency upgraded EudraVigilance, expanding its analytical capacity and enabling direct patient reporting across the European Union. This upgrade introduced advanced signal detection algorithms, making pharmacovigilance more proactive and data-driven [52].



safety surveilla

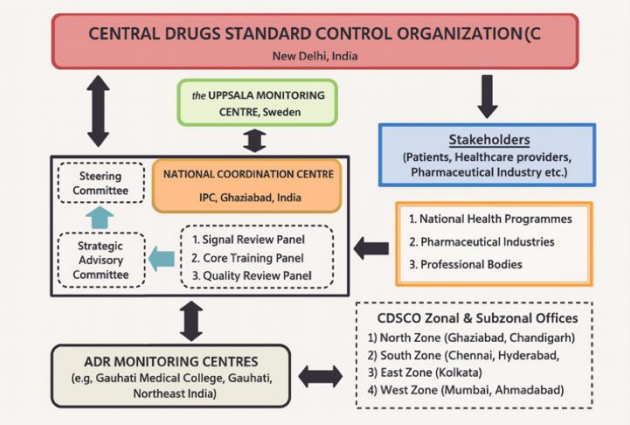
Globally, the WHO's VigiBase, maintained by the Uppsala Monitoring Centre (UMC), surpassed 35 million Individual Case Safety Reports (ICSRs) in 2023, consolidating its role as the world's largest safety dataset [53]. This allowed Bayesian and machine-learning based signal detection methods to emerge as new tools for global drug

The COVID-19 pandemic (2020–2022) provided an unprecedented stress test for global PV systems. Clinicians in Europe and Israel first reported cases of myocarditis associated with mRNA vaccines, while others noted thrombosis with thrombocytopenia syndrome (TTS) linked to adenoviral vaccines [54]. These signals were quickly published in leading journals such as The New England Journal of Medicine and The Lancet, demonstrating the critical role of frontline physicians in early detection. Regulatory agencies including the MHRA (UK), EMA (Europe), and FDA (USA) rapidly evaluated these reports, issued safety communications, and updated product information within weeks [55]. This sequence showed how clinician reports → scientific publication → regulatory action could now occur on a compressed timescale compared to previous eras.

By 2025, global pharmacovigilance has thus become digitally enabled, transparent, and increasingly powered by artificial intelligence (AI). The integration of natural language processing (NLP) tools, machine learning models, and real-world evidence platforms is shifting PV from passive detection to active prediction of risks.

> Indian Developments

India mirrored many of these global advances through the expansion of the Pharmacovigilance Programme of India (PvPI). Between 2013 and 2023, the network of Adverse Drug Reaction Monitoring Centres (AMCs) expanded from a few dozen to
nearly 895 centres across the country, covering most major teaching hospitals and
state institutions [56].
global trends.



To improve accessibility, PvPI introduced a toll-free helpline (1800-180-3024) in 2014 and a mobile application in 2015, enabling both clinicians and patients to directly report suspected ADRs [57]. This marked a significant step towards patient engagement, aligning India with

During the COVID-19 vaccination drive (2021–2022), PvPI played a central role in monitoring Adverse Events Following Immunisation (AEFIs). Indian clinicians and hospitals first documented clusters of serious events, which were then fed into the national database and shared with WHO's VigiBase. Reports related to Covishield and Covaxin were critical in confirming the safety profile of these vaccines under real-world conditions [58].

By 2023, India had become one of the largest contributors of ICSRs to VigiBase, reflecting not only the size of its population but also the increased awareness and infrastructure for ADR reporting [59]. However, challenges remain in terms of under-reporting, uneven awareness among community physicians, and limited application of AI tools compared to Western counterparts.

- **Current Situation (2025): Global vs India**

In the present decade, pharmacovigilance has transformed into a digitally enabled and real-time global system, integrating clinicians, patients, regulators, and advanced analytics.

Global perspective.
The United States and Europe have set benchmarks in terms of transparency and data accessibility. The FDA's FAERS Public Dashboard (2017) allowed direct public access to safety data, enabling researchers, clinicians, and patients to analyse ADR trends in near real time [51]. In parallel, the European Medicines Agency upgraded EudraVigilance in 2017, introducing advanced analytical tools and direct patient reporting, which reinforced public participation in drug safety [52]. On a global scale, the WHO's VigiBase surpassed 35 million reports in 2023, providing an unparalleled foundation for machine-learning–based signal detection and cross-country comparisons [53].

The COVID-19 pandemic (2020–2022) further highlighted the strength of these systems. Early signals such as myocarditis with mRNA vaccines and thrombosis with thrombocytopenia syndrome (TTS) linked to adenoviral vaccines were first noticed by clinicians, published rapidly in journals such as The Lancet and NEJM, and subsequently acted upon by MHRA, EMA, and FDA with label changes and safety communications within weeks [54–55]. This episode proved that the cycle from clinical observation to regulatory intervention had compressed dramatically compared to previous eras.

Indian perspective.

India, through the Pharmacovigilance Programme of India (PvPI), has established one of the largest national PV networks in the world, with nearly 895 Adverse Drug Reaction Monitoring Centres (AMCs) by 2023 spread across all major states and teaching hospitals [56]. To make reporting more inclusive, PvPI launched a toll-free helpline in 2014 and a mobile application in 2015, enabling both healthcare providers and patients to directly submit suspected ADRs [57].

During the COVID-19 vaccination campaign, PvPI successfully coordinated the monitoring of adverse events following immunisation (AEFIs) for Covishield and Covaxin, forwarding validated cases to the global WHO database (VigiBase). This integration not only strengthened vaccine confidence but also demonstrated India's ability to function as a major data contributor to international pharmacovigilance [58]. By 2023, India had become one of the largest national contributors of Individual Case Safety Reports (ICSRs) to VigiBase, signifying its global relevance [59].

Comparative assessment.

Globally, pharmacovigilance in 2025 is real-time, transparent, and AI-assisted, with public dashboards and strong patient engagement. India, in contrast, has built broad infrastructure and inclusive reporting channels, yet still faces challenges of under-reporting at community level, limited use of AI for signal detection, and lower public-facing transparency compared with the US and EU [57,59]. Nonetheless, PvPI's scale and integration into WHO systems mark India as a leading emerging hub of pharmacovigilance, with strong potential to close the gap in the coming decade.

♦ Pharmacovigilance Systems, Data Flow and Tools

• Systems (Global vs India)

Globally, pharmacovigilance is supported by multi-layered systems. In the United States, the FDA coordinates post-marketing safety via the FDA Adverse Event Reporting System (FAERS), integrating spontaneous reports from healthcare

professionals, patients, and marketing authorisation holders (MAHs) [60]. In Europe, the European Medicines Agency (EMA) manages EudraVigilance, a centralised electronic repository for ICSRs across member states [61]. At the international level, the WHO-Uppsala Monitoring Centre (UMC) maintains VigiBase, which aggregates data from over 140 national centres [62].

In India, pharmacovigilance is organised through the Pharmacovigilance Programme of India (PvPI), coordinated by the Indian Pharmacopoeia Commission (IPC) and overseen by the Central Drugs Standard Control Organization (CDSCO) [63]. PvPI functions through a nationwide network of nearly 900 Adverse Drug Reaction Monitoring Centres (AMCs), where reports are validated, coded, and uploaded into VigiFlow, the WHO-supported case management software [64].

- **Data Flow**

Global Model

1. Reporter (HCP/Patient) submits ADR through online forms, apps, or portals (e.g., MedWatch, Yellow Card, EudraVigilance portal) [65].
2. MAHs and local hospitals validate, de-identify, and code cases using MedDRA before forwarding [66].
3. National regulators (FDA/EMA/MHRA) triage reports, perform causality checks, and upload into regional databases [61].
4. Databases (FAERS, EudraVigilance) apply statistical algorithms (PRR, ROR, IC) to detect disproportionate reporting [67].
5. Signal management committees evaluate emerging patterns and decide actions (label changes, DHPCs, restrictions) [68].
6. Regulatory communication is made through official portals, public dashboards, and safety updates [60].
7. Reports are shared with WHO-UMC/VigiBase for global pooling [62].

- **Indian Model (PvPI)**

1. Reporter (doctor, nurse, pharmacist, or patient) submits ADR via the PvPI mobile app, AMC form, or national helpline [63].
2. AMC staff validate and code ADRs (MedDRA) and upload to VigiFlow [64].
3. National Coordinating Centre (IPC) aggregates reports, performs signal analysis, and forwards recommendations to CDSCO [63].
4. CDSCO evaluates signals and can initiate label updates, Direct Healthcare Professional Communications (DHPCs), or regulatory restrictions [69].
5. Data are simultaneously shared with WHO-UMC to enrich VigiBase and contribute to international signal detection [62].

Tools Used in Pharmacovigilance

- Reporting & Intake:
  - MedWatch (US), Yellow Card (UK), EudraVigilance portal (EU), PvPI mobile app & helpline (India) [60–63].
- Coding & Standards:
  - MedDRA (ICH-managed terminology for ADRs), WHO Drug Dictionary for medicines, ATC codes for classification [66].
- Databases:
  - FAERS (US), EudraVigilance (EU), VigiFlow (India/WHO entry system), VigiBase (WHO global repository) [61–64].
- Signal Detection Tools:
  - Disproportionality metrics (PRR, ROR, IC, EBGM) [67].
  - Platforms such as VigiLyze (WHO), Empirica Signal (Oracle), and open-source R/Python workflows for analysis [70].
- Causality Assessment:
  - WHO-UMC system, Naranjo algorithm, and specialised tools such as Brighton criteria for vaccine-related events [71].
- Risk Management:
  - PSUR/PBRER templates, Risk Management Plans (RMPs), and checklists for risk minimisation evaluation [72].
- Communication:
  - Direct Healthcare Professional Communications (DHPCs), regulatory safety alerts, and public dashboards (FDA, EMA, PvPI) [60–63].

- **Future Directions**

The future of pharmacovigilance will be defined by the integration of advanced data science methods such as artificial intelligence (AI) and machine learning for early detection of safety signals [73]. Natural language processing and big-data analytics are increasingly being applied to extract information from electronic health records, social media, and real-world evidence platforms [74]. In India, further progress depends on improving community-level ADR reporting by engaging primary care doctors, rural health workers, and pharmacists, who are often first to see adverse events [75]. Investment in automation, mobile-based tools, and AI-driven analytics will

help align Indian practices with global benchmarks [76]. Globally, harmonisation of data across jurisdictions, greater patient involvement, and transparent risk communication are needed to strengthen public confidence [77]. Collaborative models that ensure the participation of low- and middle-income countries in global systems will make pharmacovigilance more equitable and universal [78].

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♦ Conclusion

The journey of pharmacovigilance from 1848 to 2025 shows how sentinel case reports and regulatory responses gradually evolved into a structured global system [79]. Key tragedies such as the chloroform death of Hannah Greener (1848), the Elixir Sulfanilamide disaster (1937), the thalidomide catastrophe (1961), and the Vioxx withdrawal (2004) served as turning points that forced improvements in safety regulation [80]. Presently, mature systems such as FAERS (US), EudraVigilance (EU), and VigiBase (WHO) provide transparency and AI-enabled analytics [81]. India, through the Pharmacovigilance Programme of India (PvPI), has established one of the largest PV networks in the world, with nearly 895 ADR Monitoring Centres contributing regularly to global safety databases [82]. Remaining challenges include under-reporting, limited awareness at the community level, and the need for advanced analytics [83]. Ultimately, pharmacovigilance acts as the bridge between clinical care, regulatory oversight, and patient safety, ensuring that medicines retain a favourable benefit–risk balance [84].

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