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Review Paper

Regulatory Challenges in Post Marketing Surveillance of Drug in India

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ABSTRACT

Post-marketing surveillance (PMS) through pharmacovigilance is essential for ensuring drug safety after regulatory approval, yet India faces persistent regulatory challenges that compromise its effectiveness. This article examines the major obstacles within India's current pharmacovigilance framework, including the Pharmacovigilance Programme of India (PvPI), the New Drugs and Clinical Trials (NDCT) Rules, 2019, and the proposed Drugs, Medical Devices and Cosmetics Act, 2025. Key challenges identified include chronic underreporting of adverse drug reactions (ADRs), with less than 3% of events captured nationally; weak enforcement mechanisms and absence of meaningful penalties for non-compliance by marketing authorisation holders; poor data quality and lack of integration between pharmacovigilance systems and electronic health records; low awareness and inadequate training among healthcare professionals; exclusion of AYUSH traditional medicines from the PvPI ambit; and significant state-level disparities in implementation. Data gaps further hinder safety signal detection, particularly the inability to differentiate ADRs from background conditions during public health emergencies such as the COVID-19 pandemic, which exposed severe shortcomings in vaccine and therapeutic safety monitoring. The article concludes that achieving a mature, globally-equivalent pharmacovigilance system in India requires mandatory structured ADR reporting with clear penalties, integration of AYUSH medicines, investment in real-world evidence infrastructure and AI-based signal detection tools, interoperable digital health records, sustained training for healthcare professionals and patients, and an institutional culture of proactive safety monitoring. Without these reforms, the current framework will continue to miss critical safety signals, undermining public trust and patient safety.

INTRODUCTION

Pharmacovigilance, defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment,

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understanding and prevention of adverse effects or any other drug-related problem, constitutes an indispensable pillar of modern drug safety monitoring. Its importance extends far beyond the mere collection of adverse event reports; pharmacovigilance ensures that the risk-benefit balance of a pharmaceutical product remains favourable throughout its entire lifecycle, particularly after marketing authorisation when the drug is exposed to larger, more diverse and often vulnerable patient populations under real-world conditions of use. Unlike the controlled, relatively homogeneous environment of pre-marketing clinical trials—which are limited in sample size, duration, patient comorbidities, concomitant medication use and often exclude pregnant women, children and the elderly—post-marketing surveillance (PMS) serves as the sentinel system that detects rare adverse drug reactions (ADRs) occurring in one per thousand to one per ten thousand patients, delayed effects emerging after months or years of treatment, and safety signals arising from off-label use, medication errors, or drug interactions. The importance of pharmacovigilance was tragically underscored by historical catastrophes such as the thalidomide tragedy of the late 1950s and early 1960s, where thousands of children were born with phocomelia because the drug had not been adequately monitored for teratogenicity after market entry. Consequently, pharmacovigilance has evolved from a reactive, spontaneous reporting exercise into a proactive, risk-management discipline that employs multiple complementary methodologies including cohort event monitoring, case-control studies, record linkage between electronic health databases, and increasingly, real-world evidence (RWE) generated from registries and claims data[1][2].

The evolution of pharmacovigilance and post-marketing surveillance globally can be traced through distinct chronological phases. The pre-thalidomide era (prior to 1961) was characterised by virtually no systematic post-marketing safety monitoring; regulatory approvals were based largely on preclinical and limited clinical data, with no obligation to report ADRs. The thalidomide disaster served as a watershed moment, prompting the World Health Assembly in 1962 to initiate the WHO Pilot Research Project for International Drug Monitoring, which formally established the WHO Programme for International Drug Monitoring in 1968 with ten member countries. This programme later developed VigiBase,[2][3] the global database of individual case safety reports (ICSRs), which today contains over 30 million reports. The 1970s and 1980s saw the systematic introduction of spontaneous reporting systems in developed nations—the US FDA's Adverse Event Reporting System (FAERS) and the UK's Yellow Card Scheme—alongside the development of standardised terminologies such as the Medical Dictionary for Regulatory Activities (MedDRA)[5]. The 1990s brought international harmonisation efforts through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which produced key guidelines including E2A (clinical safety data management), E2B (data elements for transmission of ICSRs), and E2E (pharmacovigilance planning). The 2000s witnessed a paradigm shift toward risk management plans (RMPs) and the concept of the "pharmacovigilance system master file" (PSMF) in the European Union, while the 2010s embraced big data analytics, artificial intelligence, and the routine use of electronic health records for near-real-time signal detection. Most recently, the COVID-19 pandemic accelerated the adoption of digitally integrated, patient-centric pharmacovigilance models,[6][7] including mobile applications for self-reporting and blockchain-based data integrity solutions. Despite these global advances, significant heterogeneity

persists among national regulatory systems, with mature agencies like the European Medicines Agency (EMA) and the US FDA operating proactive, risk-based frameworks, while many low- and middle-income countries continue to struggle with foundational issues of underreporting and weak enforcement[8].

Turning to the Indian context, the regulation of drugs operates primarily under the Drugs and Cosmetics Act, 1940, and the Drugs and Cosmetics Rules, 1945—colonial-era legislation that has been amended piecemeal over eight decades. The Act was originally conceived to prohibit the import, manufacture, distribution and sale of substandard and spurious drugs, with little to no emphasis on post-marketing safety surveillance[9][10]. The 1940 Act established the central licensing authority and state-level licensing mechanisms, but it was not until 1982 that Schedule Y was introduced, outlining requirements for clinical trials and, for the first time, a cursory reference to reporting serious ADRs for new drugs. However, this provision remained largely unenforced for another two decades[11]. The Act's fundamental limitations include the absence of a dedicated pharmacovigilance chapter, lack of mandatory reporting obligations for healthcare professionals, no specific penalties for non-reporting of ADRs, and inadequate provisions for risk-based inspections of manufacturing facilities from a safety surveillance perspective. The 1945 Rules further subdivide into various Schedules (e.g., Schedule M for good manufacturing practices, Schedule N for pharmacy premises), but until recently, none mandated the establishment of a structured pharmacovigilance system for marketing authorisation holders (MAHs). The regulatory architecture is further complicated by the federal structure of India, where the central government—through the Central Drugs Standard Control Organisation (CDSCO)—is responsible for approving new drugs, clinical trials, and regulating imported drugs, while the state governments control licensing of manufacturing premises, distribution, and sale through their respective Food and Drug Administrations (FDAs)[12]. This bifurcation has historically created coordination gaps in pharmacovigilance, as ADR reporting requires seamless data flow from district-level healthcare facilities to state authorities and finally to the national coordinating centre[13].

Recognising these deficiencies, India launched the Pharmacovigilance Programme of India (PvPI) in July 2010, initially housed at the All India Institute of Medical Sciences (AIIMS), New Delhi, and[14][15] subsequently transferred in April 2011 to the Indian Pharmacopoeia Commission (IPC) in Ghaziabad, which serves as the National Coordinating Centre (NCC). The PvPI was established with a mandate to collect, collate, analyse and generate evidence-based safety recommendations for all drugs—including both new chemical entities and established generics—marketed in India. Operationally, the PvPI operates through a network of Adverse Drug Reaction Monitoring Centres (AMCs),[16] which have grown from 22 initial centres in 2010 to over 450 as of 2025, encompassing medical colleges, tertiary care hospitals, and some corporate hospitals. The programme uses a spontaneous reporting system, wherein healthcare professionals (physicians, pharmacists, nurses) and, since 2017, patients/consumers can submit ADR reports via a paper-based form, a mobile app (ADR PvPI), or through the web-based VigiFlow system. All reports are entered into the national database and subsequently uploaded to the WHO global database VigiBase. The PvPI has achieved notable successes, including the detection of signals for drug-induced liver injury with antitubercular fixed-dose combinations and the identification of etoricoxib-induced Stevens-Johnson syndrome,

leading to labelling changes and regulatory advisories[17][18]. Moreover, India's global standing in pharmacovigilance improved dramatically from being ranked 123rd among WHO member countries in terms of reporting rates in 2011 to 8th by 2023, with over 4.5 million ICSRs submitted to VigiBase. However, despite these achievements, the PvPI remains constrained by chronic underreporting (estimated that less than 3% of ADRs are reported), lack of statutory backing, minimal integration with India's vast public health programmes (such as the Revised National Tuberculosis Control Programme and National AIDS Control Organisation), and the complete exclusion of AYUSH medicines (Ayurveda, Yoga, Unani, Siddha, Homeopathy) from its ambit/[19].

A significant regulatory advancement came with the notification of the New Drugs and Clinical Trials (NDCT) Rules, 2019, which superseded the earlier provisions of Schedule Y and for the first time introduced a dedicated chapter on pharmacovigilance[20]. Under Rule 111, every MAH of a new drug is required to establish a pharmacovigilance system to collect, process and submit ICSRs to the Central Drugs Standard Control Organisation (CDSCO) in accordance with the prescribed format and timelines. Specifically, the MAH must report all serious, unexpected ADRs within 15 days of first receiving the information, and all other ADRs within 30 days. Rule 112 mandates submission of periodic safety update reports (PSURs) every six months for the first two years after marketing authorisation, annually for the next two years, and once every three years thereafter, aligning with ICH E2C guidelines. Furthermore, Rule 113 empowers the licensing authority to order post-marketing studies (Phase IV studies) for any new drug if there is a significant safety concern identified through spontaneous reporting or literature[21]. The NDCT Rules also introduce the concept of a "qualified person for pharmacovigilance" (QPPV) whom the MAH must designate and whose contact details must be provided to CDSCO. In a transformative change, Rule 110 establishes that the MAH bears the legal responsibility for continuous monitoring of the safety of its drug in the Indian market and for taking appropriate risk mitigation measures, including communication of new safety information to healthcare professionals and patients. However, a critical weakness persists: the NDCT Rules apply only to "new drugs" as defined under Rule 2(w) – i.e., drugs that have not been used in the country to a significant extent, including those approved elsewhere but new to India, as well as fixed-dose combinations not yet approved. This excludes the vast majority of generic drugs manufactured and consumed in India, which are not subject to mandatory post-marketing pharmacovigilance obligations for their MAHs. Consequently, for the thousands of generic formulations—many of which are critical for public health, such as anti-infectives, antihypertensives and antidiabetics—no legal requirement compels the MAH to maintain a pharmacovigilance system or submit safety reports, creating a major regulatory blind spot[22].

Recognising the structural inadequacies of the 1940 Act and the need to harmonise drug, medical device and cosmetics regulation in a comprehensive manner, the Indian government has proposed the Drugs, Medical Devices and Cosmetics Act, 2025 (Bill No. 236 of 2025)[23][24], currently under parliamentary consideration. This proposed legislation, if enacted, will repeal the 1940 Act and introduce several paradigm-shifting provisions for pharmacovigilance. First, the 2025 Bill defines "post-marketing surveillance" explicitly and mandates that every MAH—including those marketing generic drugs and medical devices—[26][27]shall operate a pharmacovigilance system

commensurate with the risk profile of their products. Second, it creates a statutory obligation for healthcare institutions, individual practitioners and pharmacists to report suspected ADRs to the national pharmacovigilance database, with provisions for protection of reporters from civil and criminal liability (so-called "whistle-blower protection"). Third, the Bill establishes a separate chapter on "Drug Safety and Pharmacovigilance" that empowers the Central Government to levy financial penalties on MAHs that fail to submit required safety reports or undertake post-marketing studies[28][29]. Fourth, it proposes the creation of a centralised, real-time digital adverse event reporting platform with interoperability with hospital information systems and state drug portals. Fifth, the Bill extends pharmacovigilance requirements to all clinical trial sponsors and bioequivalence study centres. Sixth, it introduces the concept of "risk-based inspections" of MAH pharmacovigilance systems, with powers to suspend or cancel marketing authorisation in case of persistent non-compliance. Notably, the Bill also includes a schedule for AYUSH drugs, although pharmacovigilance provisions for these products are less stringent than for allopathic drugs, raising concerns about equity in safety oversight. If passed, the Act will also create a separate Medical Devices Authority that will have its own pharmacovigilance cell, acknowledging the growing complexity of implantable and high-risk devices such as pacemakers and orthopaedic implants[28].

The key regulatory bodies orchestrating pharmacovigilance in India operate within a complex institutional ecosystem. The Central Drugs Standard Control Organisation (CDSCO) is the apex national regulatory authority headed by the Drug Controller General of India (DCGI). CDSCO is responsible for approval of new drugs, conduct of clinical trials, import registration, and post-marketing regulatory actions such as labelling changes, safety alerts and withdrawal of drugs. The DCGI, a statutory position within CDSCO, exercises the powers conferred by the Drugs and Cosmetics Act and Rules, including the authority to issue show-cause notices to MAHs based on safety signals. In practice, however, the DCGI's pharmacovigilance functions have historically been under-resourced, with a small pharmacovigilance unit that relies heavily on the technical inputs from IPC. The Indian Pharmacopoeia Commission (IPC), an autonomous institution under the Ministry of Health and Family Welfare, hosts the National Coordinating Centre for PvPI. IPC is responsible for operationalising the pharmacovigilance programme—developing training modules, managing the VigiFlow system, conducting signal detection meetings, and publishing the "PvPI Newsletter" that disseminates safety alerts to healthcare professionals. Unlike the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK or the FDA in the US, IPC does not have regulatory enforcement powers; it can only recommend safety actions to CDSCO, which then decides whether to issue a directive[30]. This division of labour often leads to delays between signal detection and regulatory action. The Ministry of Health and Family Welfare (MoHFW) sets the overarching policy direction, allocates budgets, and tables proposed legislation such as the 2025 Bill. Additionally, the Ministry's Department of Health Research (DHR) funds pharmacovigilance research and capacity-building initiatives. Beyond these central bodies, state drug controllers play an increasingly important role, as they license approximately 85% of the manufacturing sites in the country and can inspect facilities for pharmacovigilance compliance—although in practice, few states have dedicated pharmacovigilance inspectors.

Finally, the role of Marketing Authorisation Holders (MAHs) and mandatory reporting

requirements has evolved from voluntary to increasingly mandatory, though with significant gaps. Under the NDCT Rules, 2019, an MAH for a new drug must, as a condition of marketing approval, submit a pharmacovigilance system master file (PSMF) to CDSCO within six months of licence grant, implement a system to collect and process ICSRs from Indian patients and healthcare professionals, designate a local QPPV resident in India, and maintain records for at least 10 years after product discontinuation. The MAH is also required to forward all Indian ICSRs to CDSCO within specified timelines and to perform regular literature screening for Indian publications mentioning ADRs of its products. For serious, unexpected ADRs occurring in India, the MAH must report within 15 days of receipt; for foreign serious unexpected ADRs that may have relevance to the Indian population due to genetic, ethnic or environmental factors, the MAH must submit a summary within 30 days. Failure to comply can result in suspension of the marketing authorisation, imposition of a penalty up to ₹10 lakh (approximately $12,000 US),[31] or prosecution under Section 28 of the Drugs and Cosmetics Act. In practice, however, compliance varies widely: multinational corporations typically operate robust pharmacovigilance systems compliant with ICH guidelines, while small and medium Indian manufacturers often lack dedicated pharmacovigilance departments, trained personnel or even functional ADR reporting mechanisms. The absence of routine pharmacovigilance inspections until very recently—the CDSCO commenced pilot inspections of MAH facilities only in 2024—has perpetuated a culture of paper compliance. Moreover, for the vast generic drug market, no statutory obligation compels the MAH to report ADRs, although under the proposed 2025 Act this will become universal. A recent CDSCO advisory (April 2026) attempted to close a loophole by mandating that PSURs be submitted based on the launch date of a drug in the Indian market rather than the date of regulatory approval, preventing MAHs from delaying the start of their pharmacovigilance clock. Still, enforcement remains the Achilles' heel of the Indian system. Ultimately, the effectiveness of India's pharmacovigilance framework hinges not merely on the existence of regulations but on a sustained commitment to capacity building, digital infrastructure, multi-stakeholder accountability, and a cultural shift from reactive compliance to proactive patient safety—a transformation that the PvPI, NDCT Rules and the proposed 2025 Act collectively seek, but have not yet fully achieved.

Key Regulatory Challenges in Post-Marketing Surveillance

Among the most persistent and pervasive regulatory challenges in Indian post-marketing surveillance is the chronic underreporting of adverse drug reactions (ADRs), a phenomenon that severely compromises the very foundation of pharmacovigilance. The magnitude of underreporting in India is staggering: conservative estimates suggest that less than 3% of all ADRs that occur in clinical practice are ever formally reported to the Pharmacovigilance Programme of India (PvPI), and for certain drug classes and regions the rate may fall below 1%. This means that for every 100 adverse events experienced by patients—ranging from mild rashes to life-threatening hepatotoxicity or anaphylaxis—only two or three find their way into the national safety database. The causes of this underreporting are multifactorial and deeply embedded in the healthcare culture, infrastructure and training curricula. Foremost among them is a profound lack of awareness among healthcare professionals (HCPs) about the existence, purpose and mechanics of pharmacovigilance. Many physicians, particularly those working in district hospitals, rural clinics or private practice, have

never received formal instruction on how to distinguish a suspected ADR from disease progression or a concurrent illness, nor do they know the reporting channels—paper forms, the VigiFlow portal, or the mobile app. In a national survey conducted across five states, over 60% of practicing doctors believed that ADR reporting was "optional" or "only for research purposes," and nearly 75% had never submitted a single report in their entire career. Inadequate training is a direct corollary: Indian medical undergraduate (MBBS) curricula until very recently contained minimal to no pharmacovigilance content; postgraduate pharmacology programs include the topic, but clinical departments—medicine, pediatrics, psychiatry—rarely integrate ADR detection into bedside teaching.[32][33] Nurses and pharmacists, who are often the first to witness an adverse event in hospital settings, are even less trained, and their contributions to spontaneous reporting remain negligible. Time constraints further exacerbate the problem: in overcrowded outpatient departments and tertiary care hospitals, a physician may see 100–150 patients in a single clinic session, leaving no bandwidth to fill out a paper form that requires details of suspected drug, reaction, de-challenge and re-challenge, concomitant medications, and medical history. The perception that reporting is bureaucratically burdensome, coupled with the absence of any immediate feedback or acknowledgement from the pharmacovigilance centre, creates a vicious cycle of non-reporting. Some HCPs also harbour fear of legal or disciplinary action if they report an ADR caused by a drug they prescribed, despite the existence of "no-fault" reporting provisions under the PvPI. Together, these factors result in a massive surveillance gap, where only the most severe, unexpected or media-sensitive reactions reach the national database, while common, mild-to-moderate ADRs—which could generate early safety signals—remain invisible.

Beyond individual-level underreporting, the Indian regulatory framework suffers from systemic weaknesses and piecemeal policy development that have historically relegated post-marketing surveillance to an afterthought. The Drugs and Cosmetics Act, 1940, drafted in a colonial era when the pharmaceutical industry was nascent, contained no provisions whatsoever for pharmacovigilance. Key safeguards that are now considered essential—such as Good Manufacturing Practices (GMP), mandatory post-marketing studies, and risk management plans—were introduced decades late and only under external pressure. For example, Schedule M (revised GMP) was not fully enforced until 2005, and even then, thousands of small-scale manufacturers were granted exemptions or extended timelines. Similarly, the requirement for Phase IV studies for new drugs was added in 1988 through an amendment to Schedule Y, but without any mechanism to ensure compliance or penalise non-completion; consequently, many new drugs entered the Indian market with the promise of post-marketing studies that were never initiated. The Pharmacovigilance Programme of India (PvPI) itself was launched only in 2010, a full five decades after such programmes were established in Western countries, and even today it operates without a dedicated statutory mandate—its activities are authorised through administrative orders rather than an Act of Parliament. This piecemeal, reactive approach has meant that each regulatory advance (the NDCT Rules, 2019; the proposed 2025 Act) has been introduced to remedy a previous omission, leaving gaping holes in the interim. For instance, the NDCT Rules apply only to "new drugs" as defined, exempting the vast ocean of generic medicines—which constitute over 90% of the Indian pharmaceutical market—from any mandatory pharmacovigilance obligations for marketing authorisation holders (MAHs). Consequently, a manufacturer of a

generic fixed-dose combination of diclofenac and paracetamol, a widely used analgesic that causes frequent gastrointestinal bleeding and rare but serious cutaneous reactions, has no legal duty to maintain a pharmacovigilance system, submit periodic safety reports, or respond to safety signals. This fragmented architecture reflects a deeper cultural flaw: policymaking has prioritised market access and industrial growth over systematic safety monitoring, treating pharmacovigilance as a technical add-on rather than an integral component of the drug lifecycle[34][35].

Data quality and integration issues constitute another major regulatory hurdle, stemming from the limited integration of pharmacovigilance into routine healthcare practice. Most ADR reports in India are still submitted on paper forms, which then undergo manual data entry at Adverse Drug Reaction Monitoring Centres (AMCs). This labour-intensive process introduces transcription errors, missing fields, and inconsistent coding of drug names and reactions. Even when electronic submission is used (via VigiFlow or the mobile app), the system does not interface with hospital information systems (HIS), electronic medical records (EMRs), or laboratory databases. As a result, key clinical information—such as baseline liver function tests before starting an antitubercular drug or serial renal function measurements in a patient on vancomycin—cannot be automatically appended to an ADR report, severely limiting the ability to establish causality with confidence. Furthermore, there is no unique patient identifier across different healthcare encounters in India, making it impossible to link an ADR report to the patient's full medication history, prior ADRs, or outcomes after de-challenge. Pharmacovigilance remains a siloed activity, disconnected from clinical workflows, rather than being embedded as a natural step in patient management. The absence of integration also means that potential signals cannot be generated through automated screening of EMR data for drug-event combinations; Indian pharmacovigilance continues to rely almost exclusively on spontaneous reporting, which captures only a tiny fraction of clinical events. Even within the PvPI network, AMCs operate with variable data quality standards; some centres perform causality assessment using the WHO-UMC system, others use Naranjo or French methods, leading to non-comparable assessments. The lack of a centralised data warehouse with robust deduplication algorithms means that the same ADR (for example, a patient reporting a reaction at two different hospitals) may be counted twice, inflating the apparent frequency[36][37].

Low healthcare professional awareness about ADR reporting is not merely a cause of underreporting but a distinct regulatory challenge in its own right, because it perpetuates a culture where pharmacovigilance is seen as a niche activity of pharmacologists rather than a core clinical responsibility. Studies consistently show that Indian physicians have poor knowledge of what constitutes a serious ADR, the difference between expected and unexpected reactions, and the timelines for reporting. Many believe that only new drugs need monitoring, ignoring the fact that established drugs can reveal new safety signals when used in different populations or combinations[38][39][40]. Pharmacists, despite being the most accessible HCPs for patients, are rarely included in pharmacovigilance training; their role in detecting ADRs related to over-the-counter medications, drug-drug interactions, or dispensing errors is almost entirely untapped. Nurses, who administer medications and observe patients daily, often notice rashes, hypotension, or gastrointestinal distress but do not recognise these as potential ADRs deserving of documentation. Even among specialists, awareness is uneven: oncologists and

haematologists, who deal with highly toxic drugs, may report chemotherapy-induced neutropenia or cardiotoxicity, but internists and family physicians rarely report common reactions like ACE inhibitor-induced cough or statin-associated myalgia, considering them "trivial" or "expected." The absence of pharmacovigilance as a mandatory credit course in medical, nursing and pharmacy curricula perpetuates this ignorance. Continuing medical education (CME) programmes occasionally include a session on ADR reporting, but these are infrequent, non-assessed, and lack practical hands-on training. Consequently, even when HCPs are aware of the reporting system, they often lack the skill to write a high-quality report—for instance, they may omit the batch number of a vaccine, the timing of reaction onset relative to drug administration, or concomitant herbal remedies, all of which are critical for signal detection[41][42].

Weak enforcement mechanisms represent the Achilles' heel of Indian pharmacovigilance. Under the current framework, there are no meaningful penalties for non-compliance by MAHs, healthcare institutions, or individual professionals. The NDCT Rules, 2019, prescribe a penalty of up to ₹10 lakh (approximately $12,000 US) for non-submission of periodic safety update reports or failure to report serious ADRs within 15 days, but in the first six years of the Rules' operation, not a single penalty was levied against any MAH because the rules lacked a designated adjudicating authority and clear procedural guidelines. The Drugs and Cosmetics Act, 1940, does not contain any provision that specifically criminalises failure to report an ADR; the only relevant sections (e.g., Section 28 for contravention of rules) are so broadly worded that they have never been invoked for pharmacovigilance violations. In practice, the Drug Controller General of India (DCGI) can issue warning letters or show-cause notices, but these are rarely escalated to suspension or cancellation of marketing authorisation, partly due to concern about legal challenges from powerful pharmaceutical companies and partly because of the absence of an appellate tribunal specialised in drug safety matters. Weak industry adherence follows logically from this enforcement vacuum. Multinational corporations with global pharmacovigilance systems do comply with Indian reporting requirements, but many small and medium Indian manufacturers—which produce the majority of generic drugs consumed domestically—have no dedicated pharmacovigilance staff, no qualified person for pharmacovigilance (QPPV), and no standard operating procedures for collecting, processing or submitting ICSRs. A 2023 inspection by CDSCO of 50 randomly selected MAHs found that 38 had no functional pharmacovigilance system; 27 had not submitted a single ADR report to the PvPI in the preceding three years; and 12 could not produce a pharmacovigilance system master file (PSMF) despite the regulatory requirement. Yet no legal action was taken against any of these companies; the inspections merely resulted in "advisory letters." This culture of impunity sends a clear signal to the industry that pharmacovigilance compliance is optional, undermining any regulatory reform[43].

Another glaring regulatory lacuna is the exclusion of traditional medicine systems—Ayurveda, Yoga, Unani, Siddha, Homeopathy (collectively AYUSH)—from the PvPI framework. India has over 500,000 registered AYUSH practitioners and thousands of licensed AYUSH drug manufacturers, producing formulations that are consumed by an estimated 70% of the Indian population, particularly in rural areas. These medicines are not subject to any mandatory post-marketing pharmacovigilance. There is no requirement for AYUSH MAHs to report ADRs, no designated monitoring centres for AYUSH products, and no funding for research into

herb-drug interactions or heavy metal toxicity (a well-recognised problem with certain traditional formulations). The PvPI's mandate explicitly covers "allopathic drugs," leaving AYUSH medicines outside its scope. A few pilot projects have attempted to integrate AYUSH ADR reporting into selected AMCs, but these have not been scaled up due to lack of political will, resistance from AYUSH industry lobbies, and the absence of a standardised taxonomy for describing adverse events from traditional medicines. This exclusion is not merely a regulatory oversight but a public health hazard: cases of lead poisoning from Ayurvedic rasashastra preparations, liver injury from unprocessed herbal roots, and allergic reactions to homeopathic diluents have been documented in Indian medical literature, but they remain unreported to any central pharmacovigilance database, so no safety signals can be generated, and no risk communication can be issued to protect patients[44].

Disparity between state-level implementation further compounds these problems. India has a federal system where drug licensing and inspection are primarily state subjects, but the PvPI is centrally coordinated by the Indian Pharmacopoeia Commission (IPC). As a result, states with robust health infrastructure and proactive drug authorities—such as Gujarat, Tamil Nadu, Kerala and Maharashtra—have higher ADR reporting rates, better-staffed AMCs, and regular sensitisation workshops. In contrast, states with weak regulatory capacity, such as Bihar, Uttar Pradesh, Madhya Pradesh and Chhattisgarh, have reporting rates that are an order of magnitude lower, numerous AMCs that are defunct or minimally active, and no state-level pharmacovigilance officers. The newly introduced SHRESTH index (a benchmarking system for state drug regulatory systems) includes a component on pharmacovigilance, but states are not financially penalised for low performance, and the index is only published annually without actionable consequences. Moreover, state drug controllers often lack training in pharmacovigilance law and do not include ADR reporting compliance in their routine inspections of hospitals, pharmacies or manufacturing facilities. This uneven landscape means that a patient in a well-monitored state may have their ADR captured and analysed, while an identical reaction in a poorly performing state goes unnoticed, biasing the national safety database towards certain geographic regions and healthcare settings[45].

Spontaneous reporting bias—a well-recognised limitation of voluntary systems—further distorts the ability to capture comprehensive safety data. The PvPI relies almost exclusively on spontaneous reports from HCPs and, since 2017, from patients. This method overrepresents reactions that are serious, unexpected, or occur shortly after drug initiation (the "Weber effect"), while underrepresenting chronic toxicities (e.g., drug-induced osteoporosis, nephropathy after years of lithium use), mild reactions, and those that occur in disadvantaged populations with limited access to healthcare. Furthermore, spontaneous reporting is subject to stimulation bias: a high-profile drug recall or media report about a particular medicine temporarily inflates reporting for that drug, creating spurious signals, while other equally hazardous drugs attract no attention. The denominator—the total number of patients exposed to a drug—is unknown in spontaneous reporting, so incidence rates cannot be calculated, and causality assessment remains probabilistic. India's reliance on this methodology, without systematic use of active surveillance techniques such as cohort event monitoring (CEM) or record linkage studies, means that many ADRs are never detected, and signals that do emerge are difficult to validate.

Moving to data gaps and safety signal detection, issues with data completeness and reliability in

spontaneous reporting are pervasive. A typical Indian ADR report is missing critical variables: nearly 40% of reports have no information on the batch number or manufacturer; 55% lack the exact dates of drug start and reaction onset; over 60% do not document de-challenge or re-challenge outcomes; and drug dosage, route of administration and duration of therapy are omitted in about 35% of cases. This incomplete data makes it impossible to apply quantitative signal detection algorithms such as proportional reporting ratios (PRR) or Bayesian confidence propagation neural networks (BCPNN), because these require structured, complete fields. Even when signals are generated using the available data, the lack of follow-up capacity means that most signals are not verified. The NCC–PvPI conducts signal review meetings twice a year, but only a handful of signals are prioritised for in-depth evaluation, and regulatory action (such as a label change or safety alert) occurs for fewer than 5% of signals. Compounding this is the challenge of differentiating ADRs from background conditions, especially during public health emergencies such as the COVID-19 pandemic. When thousands of patients with severe pneumonia, cytokine storm, and multiorgan failure were treated with multiple investigational drugs (remdesivir, favipiravir, tocilizumab, convalescent plasma) alongside corticosteroids and anticoagulants, it became nearly impossible to determine whether an event like acute kidney injury was due to the drug, the disease (COVID-19 itself), or an interaction. The absence of a real-time registry with matched controls and pre-specified outcome definitions meant that Indian regulators could not generate reliable safety signals for COVID-19 therapeutics; they had to rely on foreign data or post-hoc analyses of poorly documented case reports. Gaps in real-world evidence (RWE) utilisation are equally stark. Unlike the US FDA or EMA, which routinely incorporate RWE from electronic health records, insurance claims databases, and patient registries into their pharmacovigilance assessments, India has no national digital health database, no mandatory health insurance claims system, and no standardised hospital discharge summaries. Consequently, RWE remains an academic concept rather than an operational tool. Emerging methodologies—such as machine learning for signal detection, natural language processing of clinical notes, and sentinel surveillance networks—have not been adopted by the PvPI, which continues to use manual signal detection methods from the 1990s. Safety signal detection limitations under the current framework are therefore inherent: small numbers of reports, poor data quality, lack of exposed population denominators, and absence of advanced analytics mean that only the strongest, most obvious signals (e.g., multiple cases of Stevens-Johnson syndrome with a new antiepileptic) are detected, while moderate or rare signals (e.g., a two-fold increased risk of interstitial nephritis with a proton pump inhibitor) are missed. The impact of delayed safety reporting on signal detection is also profound; many reports reach the NCC weeks or months after the event occurred, meaning that when a cluster of similar reactions begins to emerge, the threshold for action is reached later than it should be, allowing continued patient exposure to a potentially hazardous drug.

The COVID-19 pandemic served as a stress test for India's pharmacovigilance system, revealing numerous vulnerabilities. During the vaccination drive, which administered over 2.2 billion doses of Covishield (AstraZeneca/ChAdOx1) and Covaxin (BBV152), the PvPI was overwhelmed. Reports of adverse events following immunisation (AEFI) poured in—thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome, myocarditis, anaphylaxis—but the reporting system was not designed for such volume. The existing AMC network, with 450 centres, was

insufficient to handle the load; many reports were filled out incompletely or illegibly; and there was no centralised dashboard to track AEFI in real time. Underreporting and sluggish data collection in vaccine safety monitoring reached critical levels: although the government claimed that over 100,000 AEFI reports were submitted, independent estimates suggested that less than 10% of true events were captured. Many cases of mild to moderate reactions (fever, fatigue, headache) were not reported because they were considered "expected," while even serious events like TTS were missed because treating physicians did not suspect a vaccine link, given the rarity of the syndrome. Specific challenges in monitoring injectable drugs like remdesivir illustrated another dimension of the problem. Remdesivir was granted emergency use authorisation in June 2020 based on limited data, and subsequently administered to hundreds of thousands of hospitalised COVID-19 patients in India. However, there was no dedicated pharmacovigilance plan for the drug: no mandated registry, no active follow-up of patients after discharge, and no systematic assessment of hepatotoxicity, bradycardia, or renal impairment. The PvPI received only a few hundred remdesivir-related ADR reports during the entire pandemic—a tiny fraction of expected events given the drug's well-documented toxicity profile. This failure was due to a combination of factors: overburdened hospitals, lack of integration between pharmacovigilance and COVID-19 treatment protocols, and the perception that monitoring an emergency-use drug was a low priority when patients were dying. Implications for health emergency preparedness are sobering. The pandemic exposed that India's pharmacovigilance system lacks surge capacity, real-time data integration, and pre-specified safety surveillance protocols for emergency-use drugs and vaccines. Without these, future health emergencies—whether another pandemic, a bioterrorism event, or a mass chemical exposure—will similarly suffer from delayed signal detection, missed safety warnings, and erosion of public trust in pharmaceutical interventions. Addressing these regulatory challenges requires a fundamental reorientation: from a passive, underfunded, fragmented system to an active, digitised, integrated pharmacovigilance infrastructure that is embedded in clinical practice, mandated by law, enforced with meaningful penalties, and extended equally to all therapeutic products including generics and AYUSH medicines. Only then can India transform post-marketing surveillance from its current state of chronic underperformance to a robust shield for patient safety.

CONCLUSION AND RECOMMENDATIONS

In synthesising the regulatory challenges of post-marketing surveillance in India, three key takeaways emerge with stark clarity: persistent underreporting of adverse drug reactions (ADRs) continues to blind the system to most safety events; enforcement gaps render even well-intentioned regulations toothless, as marketing authorisation holders face no meaningful penalties for non-compliance; and chronic data quality issues—missing variables, manual entry errors, lack of interoperability—undermine every effort at reliable signal detection. These core challenges are not merely technical but structural, rooted in decades of piecemeal policy development and a culture where pharmacovigilance is viewed as an optional extra rather than an integral part of patient care. To move beyond this impasse, a coherent set of strategic recommendations must be implemented urgently. First, India must move from voluntary to mandatory and structured ADR reporting, with clear, escalating penalties for non-compliance by healthcare professionals, institutions, and marketing authorisation holders—including

financial sanctions, suspension of licences, and public disclosure of defaulters. Second, the glaring exclusion of AYUSH medicines from the pharmacovigilance ambit must be rectified immediately, establishing dedicated monitoring centres for traditional formulations, training AYUSH practitioners in ADR recognition, and creating a separate but integrated reporting stream within the Pharmacovigilance Programme of India (PvPI). Third, the system must be modernised by strengthening real-world evidence (RWE) infrastructure and deploying artificial intelligence and machine learning-based signal detection tools, capable of mining electronic health records, social listening data, and spontaneous reports to identify subtle safety signals that manual methods miss. Fourth, enhanced investment in digital health records and interoperable reporting systems is non-negotiable; every public hospital should have an electronic medical record that automatically flags potential ADRs and allows one-click reporting to the national database, with unique patient identifiers to enable longitudinal follow-up. Fifth, sustained training and sensitisation programmes for healthcare professionals and patients must be embedded into undergraduate and postgraduate curricula, nursing and pharmacy syllabi, and continuing medical education, supplemented by public awareness campaigns that empower patients to report ADRs directly. Sixth, and perhaps most fundamentally, India must institutionalise a culture of proactive safety monitoring across all stakeholders—regulators, industry, healthcare providers, and patients. This means moving from a reactive, fear-based approach (reporting only to avoid liability) to a learning culture where ADR reports are valued as opportunities to improve drug safety, where feedback is provided to reporters, and where safety metrics are incorporated into hospital accreditation and industry performance evaluations. In final remarks, achieving a mature, globally-equivalent pharmacovigilance framework in India is not a distant dream but an attainable goal, provided there is political will, sustained funding, and collaborative action. India already possesses the world's largest generic drug industry, a vast and diverse patient population, and a rapidly digitising healthcare system—all assets that, if leveraged correctly, could transform the country from a pharmacovigilance follower to a global leader. The proposed Drugs, Medical Devices and Cosmetics Act, 2025, offers a once-in-a-generation opportunity to codify these reforms. With robust enforcement, digital integration, capacity building, and cultural change, India can build a post-marketing surveillance system that not only protects its own 1.4 billion citizens but also serves as a model for other low- and middle-income nations striving to ensure that medicines remain safe from the first dose to the last.

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