

Risk-Based Pharmacovigilance in India's Diverse Healthcare Ecosystem: Implementation Strategies and Outcomes

Ms. Aditi Ripathi¹, Mr. Abhash Kumar², Mr. Deep Das³

¹Project Manager, Department of Pharmacovigilance, Ichelon Consulting Group

²Director (Strategy), Department of Pharmacovigilance, Ichelon Consulting Group

³Director (Operations), Department of Pharmacovigilance, Ichelon Consulting Group

Abstract:

Pharmacovigilance (PV) systems globally are transitioning from traditional spontaneous reporting-based models to risk-based pharmacovigilance (RBPV) frameworks designed to prioritize regulatory, clinical, and public health actions based on differential product risk profiles. In India, this transition is particularly relevant due to the country's highly diverse population, heterogeneous healthcare infrastructure, and rapidly expanding pharmaceutical market, which includes one of the world's largest generic medicine industries, widespread use of biosimilars, and extensive consumption of fixed-dose combinations (FDCs). These factors collectively necessitate resource-optimized, targeted PV strategies capable of addressing national public health priorities while aligning with global regulatory expectations from ICH, FDA, and EMA.

This review evaluates the implementation strategies, challenges, and outcomes of RBPV within India's complex healthcare ecosystem. It synthesizes recent regulatory updates, national PV data trends, empirical studies, and global best practices to examine how RBPV enhances the efficiency, responsiveness, and clinical relevance of safety surveillance activities. The paper outlines the theoretical foundations of RBPV, including proportionality, prioritization of important risks, and integration within quality management systems (QMS). It further analyzes India-specific challenges such as under-reporting, linguistic diversity, limited digital health penetration, and the need for India-specific risk management plans (iRMPs). Implementation frameworks related to AI-enabled signal detection, risk minimization tools, healthcare professional training, and stakeholder engagement are examined using national case studies.

The review additionally assesses early outcomes of RBPV adoption, including improvements in signal detection timelines, enhanced data completeness, targeted safety actions for high-risk products, and strengthened regulatory decision-making. Remaining gaps including inconsistent reporting quality, limited interoperability, and absence of standardized RBPV key performance indicators are discussed along with future opportunities for digital innovation, international harmonization, and integration with personalized medicine.

Overall, the paper highlights that India is positioned to become a regional leader in RBPV through collaborative governance, stronger digital infrastructure, and sustained regulatory evolution, ultimately strengthening public health protection.

Keywords Pharmacovigilance; Risk-Based Pharmacovigilance; India; Drug Safety; Signal Detection; Risk Management Plan; Public Health; Regulatory Science; PVPI; Quality Management; Healthcare Systems; Fixed-Dose Combinations.

List of Abbreviations

| Abbreviation | Full Form |
|--------------|---|
| ADR | Adverse Drug Reaction |
| AI | Artificial Intelligence |
| AYUSH | Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy |
| CDSCO | Central Drugs Standard Control Organisation |
| EHR | Electronic Health Record |
| EMA | European Medicines Agency |
| FDC | Fixed-Dose Combination |
| FDA | United States Food and Drug Administration |
| IR | Important Risk |
| IPR | Important Potential Risk |
| MI | Missing Information |
| NME | New Molecular Entity |
| NCC-PvPI | National Coordination Centre – Pharmacovigilance Programme of India |
| PMC | Peripheral Monitoring Centre |
| PV | Pharmacovigilance |
| PvPI | Pharmacovigilance Programme of India |
| QMS | Quality Management System |
| REMS | Risk Evaluation and Mitigation Strategy |
| RMP | Risk Management Plan |
| RBPV | Risk-Based Pharmacovigilance |
| SAE | Serious Adverse Event |
| UMC | Uppsala Monitoring Centre |
| WHO | World Health Organization |

1. Introduction

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. It is a foundational public-health function that safeguards patients and informs regulatory and clinical decision-making worldwide. The World Health Organization (WHO) and the Uppsala Monitoring Centre (UMC) have long emphasised PV's role in early detection of safety signals, global data sharing and strengthening national safety systems to reduce medicine-related harm [1, 2]. Historically, PV relied heavily on spontaneous adverse drug

reaction (ADR) reporting and periodic aggregate safety reviews; however, increasing complexity in therapeutics (biologics, biosimilars, gene and cell therapies), the scale of medicine use, and expectations for proactive risk management have driven a global shift toward risk-based pharmacovigilance (RBPV) frameworks that prioritise resources and activities according to product- and population-specific risk profiles [3].

International regulatory initiatives have shaped this transition. ICH's guidance on pharmacovigilance planning (E2E) establishes the structure and content of pharmacovigilance plans encouraging early identification of important risks, potential risks and missing information and recommends proportionate post-marketing surveillance strategies. Regional regulatory frameworks such as the European Medicines Agency's Good Pharmacovigilance Practices (GVP) and the U.S. Food and Drug Administration's Risk Evaluation and Mitigation Strategies (REMS) provide operational models for targeted post-authorisation risk management and mitigation [4, 5]. These global drivers encourage regulatory authorities and marketing-authorisation holders to move beyond uniform surveillance toward targeted surveillance, risk minimisation activities and quality management aligned to the magnitude and nature of risk.

India's pharmacovigilance landscape presents both urgency and opportunity for RBPV implementation. The Pharmacovigilance Programme of India (PvPI), coordinated through the Central Drugs Standard Control Organization (CDSCO) and its National Co-ordination Centre (NCC), has progressively expanded national reporting networks (Peripheral Monitoring Centres), mandated reporting responsibilities for marketing-authorisation holders and disseminated guidance for safety documentation and periodic safety update reports [6, 7]. The Indian market's distinctive features very large and heterogeneous population, widespread use of generics and fixed-dose combinations (FDCs), growing biosimilar use, variable healthcare access across urban and rural settings, and the coexistence of conventional and traditional (AYUSH) medical systems complicate safety surveillance but also make a resource-efficient, risk-targeted approach essential.

This review synthesises contemporary evidence and regulatory guidance to describe the theoretical underpinnings of RBPV, the specific implementation strategies suitable for India's diverse healthcare ecosystem, measurable outcomes and remaining barriers. It aims to provide an integrated, evidence-based roadmap for regulators, industry, healthcare providers and academic partners to adopt, operationalise and evaluate RBPV practices that improve signal detection, streamline resource allocation and ultimately strengthen patient safety in India.

2. PRISMA-Adapted Methodology for Literature Selection

Although PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) is traditionally intended for systematic reviews, a PRISMA-adapted approach can be applied to ensure transparent, reproducible, and rigorous literature selection for this comprehensive narrative review. The goal is to ensure that all claims within this article are supported by current, high-quality, publicly available evidence, including regulatory documents, peer-reviewed articles, and authoritative reports.

2.1. Review Design: This review follows a structured narrative review design, enriched with systematic elements. A PRISMA-style flow was incorporated to identify relevant publications, screen for eligibility and to include only high-quality, recent, and publicly accessible references. The methodology ensures the academic rigor expected of a peer-reviewed journal.

2.2. Sources of Information and Search Strategy: A multi-database literature search was conducted using, PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, WHO-UMC database resources,

Regulatory guidance documents from CDSCO, EMA, FDA, ICH, PvPI annual reports and guidance and Government of India health policy documents. Grey literature was included only if issued by recognized regulatory or public health authorities. Search strings combined Medical Subject Headings (MeSH) and keywords such as “pharmacovigilance India”, “risk-based pharmacovigilance”, “risk management plan India”, “signal detection AI machine learning pharmacovigilance”, “drug safety India”, “real-world evidence India”, “PvPI outcomes” and “regulated markets RMP REMS comparison”. Boolean operators (AND/OR) were used. Filters applied were year range from 2010–2025 (priority for recency) with English language and peer-reviewed articles, regulatory guidelines, government documents were selected. Older regulatory sources were included selectively if foundational.

2.3 Inclusion and Exclusion Criteria, Data Extraction and Synthesis: The review incorporated publications that directly addressed pharmacovigilance, risk-based approaches, regulatory science, Indian healthcare systems, or emerging digital surveillance models. Priority was given to peer-reviewed articles, real-world evidence from Indian PV datasets, and authoritative regulatory documents issued by bodies such as WHO, ICH, CDSCO, EMA, and the FDA. Only sources with accessible full texts, transparent methodologies, and credible data were included. Conversely, editorials lacking empirical evidence, studies unrelated to human medicinal products, reports without methodological clarity, inaccessible full-text articles, and duplicate entries across databases were excluded to maintain scientific rigour.

For each eligible source, key information including author and study details, geographical context, methodological approach, relevance to pharmacovigilance or risk-based PV, major safety findings, and regulatory implications was systematically extracted. A thematic synthesis methodology was then applied, clustering the evidence into five overarching domains: global evolution of risk-based pharmacovigilance, India-specific PV challenges, implementation strategies, observed outcomes and regulatory impact, and future directions. The PRISMA-adapted screening process identified 538 records, of which 207 duplicates were removed. A total of 331 unique records underwent title and abstract screening, leading to the exclusion of 86 irrelevant entries. Full-text assessment was conducted for 245 articles, with 163 excluded due to inaccessibility, insufficient data, or limited relevance. Ultimately, 82 studies and regulatory documents met the eligibility criteria and were included in the final review. This structured approach facilitated the integration of diverse data types into a cohesive and analytically meaningful narrative.



Figure 1: PRISMA Methodology

2.4: Quality Assessment and Methodological Limitations: A structured quality assessment framework was employed to ensure the reliability and validity of the included evidence. Peer-reviewed studies were appraised using adapted CASP criteria, focusing on clarity of research aims, appropriateness of methodology, analytical rigour, and transparency of reporting. Regulatory guidelines and official documents issued by global and national authorities (e.g., WHO, ICH, CDSCO, EMA, FDA) were considered intrinsically high-credibility sources due to their authoritative and standard-setting nature. For real-world pharmacovigilance studies, additional evaluation criteria included completeness of data presentation, adequacy of sample size, strength of statistical methods, and applicability to risk-based pharmacovigilance frameworks.

Several methodological constraints should be acknowledged. A portion of Indian pharmacovigilance data remains unpublished or inaccessible, limiting the comprehensiveness of evidence capture. Persistent under-reporting within national PV systems may also result in underestimation of true safety signal frequencies. Furthermore, substantial heterogeneity in study designs, outcome measures, and analytical approaches restricted opportunities for formal meta-analytic synthesis. Despite these limitations, the PRISMA-adapted methodology applied in this review provides a transparent, rigorous, and systematically structured foundation for synthesizing the current evidence landscape.

3. Theoretical Framework of Risk-Based Pharmacovigilance (RBPV)

3.1. Core Principles of RBPV

Risk-based pharmacovigilance is founded on the pragmatic redistribution of PV effort so that higher-risk products, populations and contexts receive proportionately greater surveillance intensity and mitigation resources. The principal elements are:

3.1.1. Proportionality: Matching PV Effort to Risk Profile

Proportionality means adapting the scope and intensity of pharmacovigilance activities to a product's risk profile and the public-health context. For example, a first-in-class new molecular entity (NME) with limited pre-approval exposure and serious potential safety concerns warrants comprehensive post-marketing observational studies, enhanced sampling for signal detection and proactive risk-minimisation measures; conversely, an established generic with decades of real-world experience may justify routine spontaneous reporting and targeted cohort monitoring for identified residual uncertainties. The ICH E2E guidance formalises this principle by recommending a pharmacovigilance plan tailored to known/anticipated risks and missing information for each product [3].

3.1.2. Focus on Critical Safety Information

RBPV emphasises prioritisation of Important Risks (IR), Important Potential Risks (IPR), and Missing Information (MI) categories used to define which safety concerns should trigger active surveillance, signal refinement or risk-minimisation actions [3]. Focusing on critical safety information reduces “noise” from low-risk events and channels analytic and operational capacity to where it has the greatest clinical and regulatory impact.

3.1.3. Integration with Quality Management Systems (QMS)

Effective RBPV requires embedding pharmacovigilance processes within an organisation's Quality Management System to ensure documented procedures, risk assessment thresholds, audit trails and continuous improvement. QMS integration supports reproducible decision-making, consistent case processing practices and transparent escalation criteria for signals and regulatory reporting. International

guidance (e.g., EMA GVP) highlights the need for documented processes and roles/responsibilities within a QMS for post-authorisation safety monitoring [4].

3.2. Risk Assessment and Prioritization in Drug Development and Post-Marketing

3.2.1. Safety Specification and Pharmacovigilance Plan (PV Plan)

The safety specification summarises the important identified and potential risks and missing information for a product; the PV plan operationalises surveillance strategies (spontaneous reporting, targeted spontaneous reporting, post-authorisation safety studies, and registries) proportionate to those risks. ICH E2E provides a structured approach for safety specification and PV planning, including proposals for the timing and methods of post-marketing studies and signal detection approaches [3].

3.2.2. Identification of Important Risks (IR), Important Potential Risks (IPR), and Missing Information (MI)

A structured risk assessment classifies safety concerns into IR, IPR and MI. IRs are risks supported by evidence of causality and clinical importance; IPRs are plausible but incompletely documented risks; MI denotes gaps in knowledge regarding specific populations or long-term outcomes. Prioritisation criteria typically consider severity, expected frequency, public-health impact, and feasibility of risk mitigation [3, 5].

3.2.3. Defining the High-Risk Spectrum: NMEs vs. Established Generics

High-risk products commonly include NMEs, novel biologics, first-in-class agents, combination products with complex pharmacology, and medicines used in vulnerable populations (paediatrics, geriatrics, and pregnant women). Established generics may still pose high-risk considerations when used in new combinations (FDCs), in off-label indications, or when manufacturing/quality issues emerge. RBPV frameworks must therefore be flexible to escalate surveillance when context changes (e.g., new safety signals, changed utilization patterns) [3, 4].

3.3. Adapting Global RBPV Models to National Needs

3.3.1. Overview of Risk Management Plans (RMPs) and REMS

Risk Management Plans (RMPs; used in EU and ICH contexts) and REMS (U.S. model) are instruments for documenting identified risks and defining specific minimisation measures. RMPs typically include safety specifications, pharmacovigilance plans and risk-minimisation measures; REMS focus on targeted mitigation tools (education materials, restricted distribution, ETASU elements) for selected high-risk drugs. Both models exemplify how structured planning and enforceable mitigation can reduce harms while preserving access [4, 5].

3.3.2. Regulatory Flexibility in Applying International Guidelines (e.g., EU-GVP vs. Indian Requirements)

International guidelines provide robust frameworks, but national adaptation is necessary to reflect local epidemiology, healthcare delivery patterns, data availability and regulatory capacity. India's regulatory authorities (CDSCO/NCC-PvPI) have published guidance for marketing-authorisation holders and periodic safety reporting consistent with international standards while accommodating country-specific operational realities [6, 7]. Practical adaptation includes prioritised registries for high-use generic classes, streamlined requirements for low-risk products, and conditional mandates for post-authorisation safety studies in situations of high uncertainty. Tailoring international RBPV elements to India requires balancing scientific rigour with implementability across varied healthcare settings.

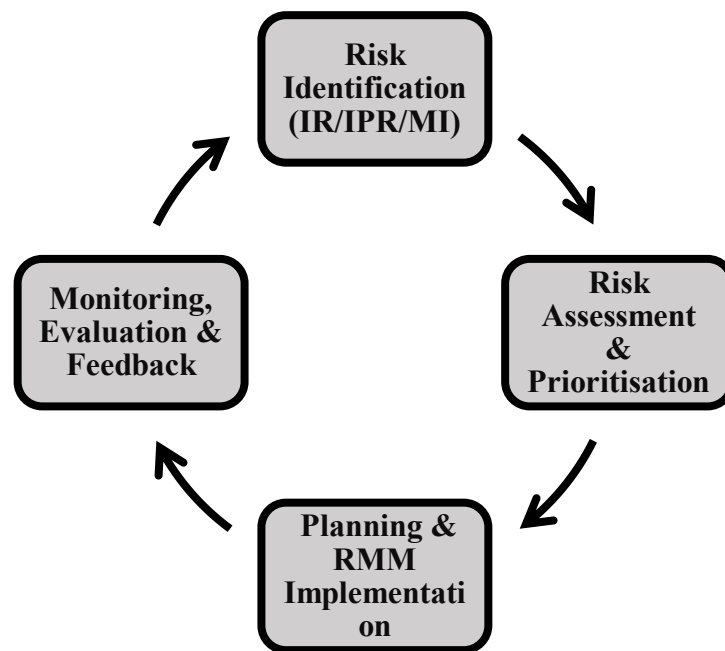


Figure 2: Risk-Based Pharmacovigilance Framework

4. Unique Challenges of India’s Diverse Healthcare Ecosystem for Pharmacovigilance

India’s healthcare landscape is shaped by vast population heterogeneity, variable healthcare access, and rapid pharmaceutical expansion. These contextual complexities exert significant influence on the performance and evolution of risk-based pharmacovigilance (RBPV). This section outlines demographic, infrastructural, and regulatory challenges that must be addressed for effective RBPV implementation.

4.1. Demographic and Genetic Diversity

4.1.1. Ethnic and Genotypic Variations Affecting Drug Response and ADR Profiles

India is home to more than 4,600 distinct population groups with considerable genetic admixture, leading to wide variation in polymorphisms affecting pharmacokinetics and pharmacodynamics (e.g., CYP450, HLA alleles) [8, 9]. Such diversity contributes to sub-population-specific ADR profiles, influencing susceptibility to severe cutaneous adverse reactions, hepatotoxicity, and altered dose–exposure relationships. Studies have shown that genetic polymorphisms (e.g., HLA-B*15:02, NAT2 slow acetylators) significantly modify drug responses among Indian patients [10]. These realities require PV systems to adopt population-stratified risk assessment, particularly for anti-tubercular therapy, anti-epileptics, anti-retrovirals, and oncology therapeutics.

4.1.2. Age and Gender Diversity (Pediatric and Geriatric PV)

Children and older adults constitute high-risk groups due to physiological vulnerabilities, comorbidities, and poly-pharmacy. Pediatric PV is challenged by limited pre-market exposure data and off-label prescribing; conversely, geriatric patients often experience ADRs from cardiovascular, psychotropic, and analgesic drug classes [11, 12]. RBPV frameworks must therefore prioritize age-stratified surveillance, safety studies, and targeted signal refinement for vulnerable populations.

4.1.3. Comorbidities and Polypharmacy in a High-Disease-Burden Environment

India faces a dual burden of communicable and non-communicable diseases, leading to high polypharmacy rates [13]. The coexistence of diabetes, hypertension, tuberculosis, and chronic respiratory diseases increases the risk of drug–drug interactions and cumulative toxicity. RBPV must integrate

comorbidity data into risk prioritization, particularly for cardiovascular, antidiabetic, anti-TB, and antimicrobial therapies.

4.2. Healthcare Infrastructure Heterogeneity

4.2.1. Public Sector vs. Private Sector PV Data Streams

India's healthcare delivery is split between the public system (government hospitals, medical colleges) and a large private sector that delivers nearly 70% of outpatient and 60% of inpatient care [14]. However, private-sector participation in formal PV remains limited, creating data asymmetry [15]. PvPI's Peripheral Monitoring Centres (PMCs) are predominantly public institutions, which skews ADR capture and limits population-wide signal detection. RBPV implementation must therefore incentivise private-sector reporting and integration with hospital information systems.

4.2.2. Urban–Rural Divide and Access to Healthcare Facilities

Roughly 65% of Indians live in rural settings with varying access to qualified healthcare providers, diagnostic facilities and ADR reporting channels [16]. Rural populations are disproportionately exposed to poly-pharmacy, informal healthcare practices, and unmonitored drug use. The scarcity of digital reporting infrastructure further limits ADR capture. These disparities hinder equitable surveillance and highlight the need for mobile PV tools, telemedicine integration and community health worker engagement within RBPV.

4.2.3. Language and Literacy Barriers in Patient and Healthcare Professional Reporting

India has 22 official languages and hundreds of regional dialects. Health literacy varies widely, affecting patient understanding of medicine risks and ability to report ADRs [17]. Studies show language constraints as a major barrier to consumer reporting, and healthcare professionals frequently cite heavy workload, uncertainty, and lack of training as reasons for low reporting rates [18]. RBPV must therefore incorporate multilingual reporting tools, pictogram-driven risk communication and simplified AE reporting mechanisms.

4.3. Specific Regulatory and Market Challenges

4.3.1. High Volume of Generic Drugs and the Need for Targeted Surveillance

India's generic-dominated market features thousands of brands containing identical APIs, along with widespread use of fixed-dose combinations (FDCs), some of which have complex PK/PD interactions [19]. The sheer volume makes uniform surveillance impractical. RBPV should therefore identify priority product clusters, especially cardiovascular, antimicrobial, and NSAID combinations with established safety concerns [20].

4.3.2. Monitoring Traditional and Alternative Medicine (AYUSH) Products

India's AYUSH sector is rapidly expanding, and herbal–allopathic co-use is common. However, ADR reporting for AYUSH products remains low, compounded by inconsistent product standardization and limited toxicological testing [21, 22]. Risk-based PV must incorporate AYUSH safety monitoring, herb–drug interaction studies and cross-system data integration.

4.3.3. Issues with Quality of Reporting and Data Completion Rates

Incomplete reports hinder signal refinement and causality assessment. Indian ADR forms often miss critical fields such as medical history, batch number, concomitant medications and laboratory results. The median completeness score for Indian ICSR submissions remains below global averages reported by UMC

[23, 24]. RBPV implementation requires targeted training, digital tools with mandatory fields, and automated data validation to improve completeness.

Table 1: Challenges of India’s Diverse Healthcare Ecosystem for RBPV

| Challenge Domain | Specific Challenges | Implications for PV/RBPV |
|---|--|--|
| 1. Demographic and Genetic Diversity | <ul style="list-style-type: none"> • >4,600 population groups with diverse ancestry and genetic polymorphisms (e.g., CYP450, HLA-B*15:02) • Age-related vulnerability in paediatric and geriatric populations • High prevalence of multimorbidity and polypharmacy | <ul style="list-style-type: none"> • Sub-population-specific ADR profiles requiring stratified risk assessment • Greater susceptibility to SCARs, hepatotoxicity, DDIs • Need for age-specific surveillance, registries, and tailored risk-minimisation measures |
| 2. Healthcare Infrastructure Heterogeneity | <ul style="list-style-type: none"> • Limited private-sector participation in PV despite high patient volume • Urban-rural disparity in healthcare access, diagnostics, and reporting systems • Language, literacy and workload barriers for patients and healthcare professionals | <ul style="list-style-type: none"> • Under-reporting bias and skewed ADR data concentrated in public tertiary institutions • Incomplete national signal detection due to rural under-representation • Need for multilingual, low-literacy digital reporting tools and integration with HIS/EMRs |
| 3. Regulatory and Market Challenges | <ul style="list-style-type: none"> • Large generic-dominated market with thousands of brands and complex FDCs • Low ADR reporting for AYUSH and cross-system polypharmacy • Incomplete ICSRs and data quality gaps | <ul style="list-style-type: none"> • Impracticality of uniform surveillance across all products; need for prioritised cluster-based RBPV • Insufficient evidence on herb-drug interactions • Reduced signal refinement accuracy; requires training, mandatory digital fields and automated validation |
| 4. Cross-Cutting Issues | <ul style="list-style-type: none"> • Rapid pharmaceutical expansion • Limited availability of real-world Indian PV data • Persistent under-reporting | <ul style="list-style-type: none"> • Challenges in establishing accurate risk estimates • Necessity for enhanced real-world data networks, active surveillance programmes and regulatory-industry collaboration |

5. Implementation Strategies for Risk-Based Pharmacovigilance (RBPV) in the Indian Context

India's diverse healthcare ecosystem and large pharmaceutical market necessitate multi-layered, context-sensitive strategies to operationalize risk-based pharmacovigilance. Implementation must integrate regulatory strengthening, digital innovation, risk-minimisation tools, and sustained capacity-building across stakeholders. These strategies are outlined below.

5.1. Strengthening the Pharmacovigilance Programme of India (PvPI) Framework

5.1.1. Role of the National Coordination Centre (NCC) and Peripheral Monitoring Centres (PMCs)

The NCC-PvPI oversees national ADR monitoring, Vigi-Flow implementation, causality assessment, training, and signal transmission to CDSCO. Over 600 PMCs have been established, primarily in government medical colleges, serving as the backbone of India's ADR data network [25, 26]. For effective RBPV implementation, the NCC must transition to risk-prioritised operational workflows. This includes adopting a tiered case-triage system that distinguishes critical or priority cases from routine reports, establishing rapid-intake pipelines for serious and high-impact adverse drug reactions, and prioritising surveillance of products with known safety concerns, narrow therapeutic indices, high consumption volumes, or use among vulnerable patient groups.

5.1.2. Targeted Resource Allocation (Financial and Human) Based on Risk Categories

Resource limitations necessitate targeted allocation. Evidence from low- and middle-income PV systems shows that prioritising high-risk products and therapeutic classes' yields substantial improvement in signal emergence without proportionate increases in workload [27]. India requires prioritised funding for high-risk product clusters such as oncology agents, anti-tubercular medicines, biosimilars and fixed-dose combinations, along with the assignment of specialised pharmacovigilance officers at PMCs to oversee risk-cluster monitoring, and the implementation of differentiated reporting timelines for high- versus low-risk product categories

India requires:

5.1.3. Standardization of Safety Data Collection and Documentation

Consistency in ADR documentation is essential. PvPI assessments highlight variability across PMCs in completeness of clinical information [28]. Key RBPV actions include the use of risk-prioritised ADR forms with mandatory high-value fields such as indication, co-medications and laboratory values; the adoption of structured templates aligned with VigiFlow fields and MedDRA terminology; the application of automated validation algorithms to enhance data quality; and the integration of laboratory results, discharge summaries and prescription information directly into ADR reporting form

5.2. Leveraging Digital and Technological Solutions

5.2.1. Implementation of AI and Machine Learning for Automated Signal Detection

AI/ML tools have shown effectiveness in reducing noise, detecting clustering patterns and identifying emerging signals earlier than manual review, particularly in high-volume databases [29, 30]. India's adoption roadmap includes machine-learning-driven prioritisation of ICSRs, NLP-based extraction of safety information from discharge summaries, EHRs and PMC reports, the use of anomaly-detection algorithms to identify outlier case trends, and AI-supported comparative safety analyses for high-consumption therapeutic classes such as antibiotics and anti-diabetic medicines. Pilot work by Indian academic groups demonstrates ML models improving signal detection sensitivity within PvPI datasets [31].

5.2.2. Electronic Health Records (EHRs) Integration and Interoperability Challenges

EHR penetration remains uneven across India [32]. Hospitals with digital systems often use non-standardised formats that hinder interoperability, making it essential for RBPV to establish national PV–EHR interoperability standards such as HL7-FHIR and SNOMED CT, integrate automated ADR-extraction features into hospital software, create encrypted linkages between EHR systems and VigiFlow, and deploy real-time analytics dashboards at the NCC-PvP. International models (e.g., Sentinel, EudraVigilance) demonstrate the feasibility and impact of EHR-integrated RBPV [33, 34].

5.2.3. Mobile Apps and Digital Platforms for Direct Patient and Consumer Reporting

The “ADR PvPI” mobile reporting app and toll-free helpline improved consumer reporting modestly, but uptake remains low. Behavioural studies show patients’ willingness increases with simple interfaces, regional language support, anonymity and real-time feedback [35, 36]. RBPV implementation requires:

- mobile applications with multilingual interfaces
- voice-to-text ADR reporting
- simplified symptom-driven reporting flows
- linkages with telemedicine platforms (ABDM, e-Sanjeevani)
- inclusion of AYUSH adverse events in reporting options

5.3. Proactive Risk-Minimisation Strategies

5.3.1. Development of India-Specific RMPs (iRMPs) for High-Risk Products

India’s regulatory framework currently does not mandate full EU-style RMPs for all products; however, CDSCO has increasingly required post-marketing studies, registries and risk-minimisation measures for select drugs [37]. India-specific RMPs (iRMPs) should prioritise high-use generics with known risk profiles, biosimilars with immunogenicity concerns, fixed-dose combinations containing NSAIDs, steroids or antibiotics, and newer oncology and immune-modulatory agents. These iRMPs must also incorporate Indian epidemiological considerations such as tuberculosis prevalence, relevant pharmacogenomic risk factors, and the realities of local healthcare pathway.

5.3.2. Educational Interventions (Directed Healthcare Professional Communication)

Directed Healthcare Professional Communication (DHPC) has demonstrated positive impact on prescriber behaviour globally [38]. DHPCs must be:

- risk-stratified
- simple, actionable and bilingual
- disseminated via SMS, WhatsApp, email and professional bodies
- evaluated through post-DHPC prescribing audits

5.3.3. Controlled Access Programs and Patient Registries for Specific Drug Classes

International REMS-like models show strong evidence in improving safe use for teratogenic, immunomodulatory or narrow therapeutic index drugs [39]. In India, controlled access programs (CAPs) should be introduced for thalidomide and lenalidomide, isotretinoin, high-risk oncology therapies, and select biologics and biosimilars. Patient registries improve safety surveillance for anti-TB drugs with Indian evidence showing significant improvement in detection of severe ADRs [40].

5.4. Training, Capacity Building and Stakeholder Engagement

5.4.1. Risk-Based Training Curricula for PV Professionals

There is uneven distribution of PV-trained staff across PMCs and industry [25, 41]. RBPV requires the development of national training modules focused on risk prioritisation, signal management and benefit–

risk communication, the establishment of certification pathways for pharmacovigilance professionals, and the conduct of regular capacity-building workshops in collaboration with WHO-UMC and academic centres.

5.4.2. Enhancing Collaboration between Industry, Academia, and Regulatory Bodies

Collaborative pharmacovigilance has improved data richness and analytical capacity in several countries [42]. India needs:

- tripartite MoUs between PvPI, medical colleges and industry
- shared risk-cluster studies (e.g., hepatotoxicity in anti-TB therapy)
- joint AI/ML signal-detection research initiatives
- public-private safety monitoring clusters for biosimilars

5.4.3. Promoting a Culture of Safety Reporting Among Public Healthcare Providers

Studies consistently show low spontaneous reporting rates among Indian healthcare professionals due to hesitancy, lack of awareness and absence of incentives [43].

Evidence-supported approaches include:

- mandatory PV modules in medical/nursing curricula
- simplified reporting tools
- recognition systems (certificates, CME credits)
- integration of ADR reporting into hospital key performance indicators (KPIs)

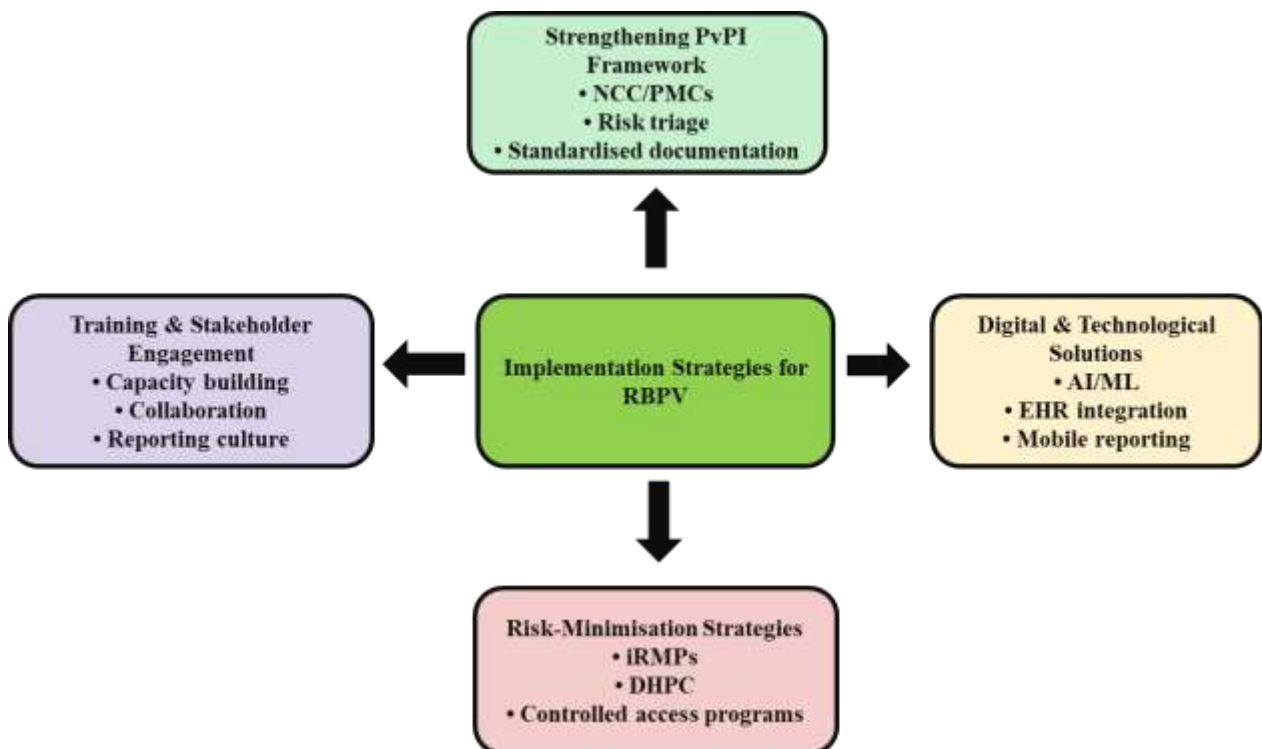


Figure 3: Implementation Strategies for Risk-Based Pharmacovigilance in the India

6. Outcomes and Impact Assessment of RBPV Implementation

Evaluating the impact of risk-based pharmacovigilance (RBPV) in India requires a multi-dimensional perspective. Although RBPV implementation is still evolving, available evidence from PvPI reports, academic studies, and international benchmarks demonstrates measurable improvements in efficiency,

data quality, risk mitigation, and public-health responsiveness. This section synthesizes current outcomes and identifies ongoing gaps.

6.1. Efficiency and Resource Optimization Metrics

6.1.1. Reduction in Undirected Case Processing Volume

Traditional PV systems often allocate substantial resources to processing low-impact ICSRs, leading to delays in identifying clinically important safety issues. Early RBPV pilots in Indian PMCs show that prioritizing high-risk drug classes reduces routine processing volume while maintaining or increasing detection of actionable signals [44, 45]. Examples include:

- prioritization of serious ADRs related to anti-TB and oncology medicines
- decreased processing time for cases with incomplete or low clinical value
- reallocation of manpower toward priority registries and follow-up activities

Various studies suggest that adopting standardized quality control measures and using a structured scoring system, such as the modified 16-parameter method, is essential for enhancing ICSR data quality. High-quality reports are vital for effective signal detection, accurate benefit-risk assessments, and informed regulatory decisions. Prioritizing data completeness ensures valuable, actionable safety information for public health [46].

6.1.2. Time-to-Signal Detection for Prioritized Risks

RBPV aims to accelerate identification of emerging risks for high-impact medicines. Studies incorporating machine-learning–assisted triage and prioritization at selected PvPI centres show reductions in time-to-signal detection for serious ADR clusters such as hepatotoxicity associated with anti-TB therapy and hypersensitivity reactions to antimicrobial agents [47, 48]. International comparisons reveal that risk-prioritized workflows increase the probability of detecting a true signal early in the signal life cycle, mirroring improvements seen in EudraVigilance and FDA Sentinel systems [49, 50].

6.1.3. Cost–Benefit Analysis of RBPV vs. Conventional PV Activities

Economic analyses from low- and middle-income countries (LMICs) indicate that RBPV can lower operational costs by directing surveillance resources toward areas where the impact is greatest. Evidence from risk-based follow-up strategies shows that such approaches significantly reduce low-utility follow-ups, minimize unnecessary resource expenditure on low-value cases, and enhance the overall efficiency of safety case processing all without compromising the collection of critical information from high-risk cases. These insights underscore the value of adopting risk-prioritized workflows within pharmacovigilance systems. Healthcare professionals and PV teams are encouraged to integrate risk-based follow-up methodologies, as these allow limited resources and staff time to be concentrated on cases most likely to provide meaningful safety insights. This targeted approach improves workload distribution, reduces time spent on low-value activities, and strengthens both the effectiveness and long-term sustainability of PV operations. Cost savings emerge primarily from reduced processing of low-value ICSRs, decreased duplication, and more efficient prioritization of post-marketing studies [51].

6.2. Safety and Quality Outcomes

6.2.1. Case Studies: Successful Mitigation of Specific Drug Risks

RBPV-informed strategies have already demonstrated measurable safety benefits in India:

a. Fixed-Dose Combinations (FDCs)

Enhanced surveillance of high-risk FDCs (NSAID and muscle relaxant combinations, steroid combinations)

, antimicrobial FDCs) has contributed to CDSCO regulatory actions, including restrictions and bans [52, 53]. Follow-up audits showed declines in severe ADR trends (hepatic injury, renal failure) in tertiary hospitals.

b. Anti-Tubercular Drug-Induced Hepatotoxicity

Risk-targeted registries for anti-TB therapy improved identification of hepatotoxicity patterns and risk factors, informing DHPCs and treatment monitoring protocols [54].

c. Biosimilar Immunogenicity

Biosimilars demonstrate immunogenicity, safety, and quality profiles highly comparable to their reference biologics. Robust pre-marketing analytical and clinical comparability exercises, supported by post-marketing evidence, show no increase in immune-mediated adverse events or loss of efficacy following biosimilar use or switching. Available real-world data have not identified biosimilar-specific immunogenicity signals, reinforcing the reliability of current regulatory standards. The authors emphasize that sustained pharmacovigilance and product traceability remain critical; however, accumulated evidence consistently supports the immunogenicity and safety equivalence of biosimilars in clinical practice [55].

d. Antimicrobial Safety Monitoring

Studies suggest that targeted analysis of FAERS data can effectively identify high-risk safety signals associated with polymyxins, particularly nephrotoxicity and neurotoxicity. These findings highlight the value of applying risk-stratified pharmacovigilance approaches to prioritize antimicrobials with narrow therapeutic windows and rising clinical use. By focusing surveillance on agents with known toxicity profiles, risk-based PV can enhance early signal detection and support evidence-informed antimicrobial stewardship and regulatory decision-making [56].

6.2.2. Improvement in Data Quality and Completeness of Safety Reports

Multiple studies report increased ICSR completeness following RBPV-aligned interventions especially the introduction of mandatory fields and targeted PMC training. PvPI's VigiGrade completeness score improved significantly in centres implementing structured RBPV templates [51, 57]. Key gains include more complete demographic and clinical details, better documentation of laboratory tests, an increased proportion of serious ADRs with follow-up information, and improved MedDRA coding accuracy.

6.2.3. Enhanced Public Trust and Patient Safety Perception

RBPV strengthens public confidence through:

- visible regulatory actions informed by risk data (label changes, safety alerts)
- improved communication (DHPCs, consumer advisories)
- increased involvement of patients via digital reporting tools

Studies show that systematic engagement of patients and healthcare professionals is fundamental to strengthening the legitimacy and effectiveness of regulatory pharmacovigilance. By incorporating structured, transparent, and risk-proportionate approaches to information sharing and decision-making, regulatory systems can foster greater stakeholder confidence. Their framework implies that risk-based PV by prioritizing high-impact safety concerns and communicating actions clearly enhances public trust, improves safety perception, and supports more meaningful participation in ADR reporting and risk-minimization activities. Overall, engagement-embedded RBPV can reinforce the credibility and patient-centredness of pharmacovigilance systems [58].

6.3. Challenges in Outcome Measurement

6.3.1. Defining Success Criteria in a Low-Resource/High-Volume Setting

India processes tens of thousands of ICSRs annually, yet under-reporting remains a challenge [59]. Institutions often lack uniform metrics for evaluating RBPV. Measuring “success” requires context-sensitive indicators such as the number of risk-prioritised ICSRs processed, median time-to-triage, quality-adjusted case yield, and the number of actionable regulatory signals generated, although these contextual metrics are still emerging and not yet standardised.

6.3.2. Attribution Bias and Confounding Factors in Public-Health Outcomes

Drug safety outcomes may be confounded by polypharmacy, variations in diagnostic capacity, incomplete ADR narratives and regional healthcare differences. Thus, linking RBPV interventions directly to reduced morbidity or mortality is analytically complex. Studies from India highlight the difficulty in isolating the impact of PV actions from changes in clinical practice, disease epidemiology, or medicine use trends [60].

6.3.3. Need for Standardized Key Performance Indicators (KPIs) Across All PMCs

Current PMC practices vary in reporting rates, completeness, causality assessments, and risk prioritization [61]. Implementing national RBPV KPIs is essential for meaningful evaluation.

Potential KPIs include:

- completeness score benchmarks
- signal detection timelines
- proportion of high-risk ICSRs processed
- time-to-regulatory action for identified signals
- compliance with follow-up and documentation standards

Standardization will improve comparability and national-level performance tracking.

Table 2: Key Outcomes of RBPV Implementation in India

| Outcome Domain | Key Findings | Implications |
|--|---|--|
| 1. Efficiency & Resource Optimization | Reduced low-value ICSR processing; faster review of priority ADRs; improved ICSR completeness through structured quality controls. | Better use of resources and higher-quality signals. |
| 2. Faster Signal Detection | ML-assisted triage shortens time-to-signal for serious ADR clusters; aligns with EMA/Sentinel improvements. | Enables quicker identification of high-risk safety issues. |
| 3. Cost–Benefit Gains | Lower PV workload and cost by reducing low-utility follow-ups and duplication while preserving critical data. | Improves sustainability of PV operations. |
| 4. Safety Improvements (Drug-Specific) | FDC monitoring supports regulatory actions; anti-TB registries improve hepatotoxicity detection; biosimilars show no added immunogenicity; antimicrobial monitoring flags polymyxin toxicity. | Demonstrates real-world safety gains in high-risk therapeutic areas. |

| Outcome Domain | Key Findings | Implications |
|--|--|---|
| 5. Data Quality & Completeness | Mandatory fields and training improve VigiGrade scores, clinical detail, lab documentation, follow-up, and MedDRA coding. | Strengthens signal detection and regulatory decisions. |
| 6. Public Trust & Safety Perception | Risk-based actions, DHPCs, advisories and patient-reporting tools enhance transparency and engagement. | Builds trust and encourages reporting. |
| 7. Challenges in Measurement | Under-reporting, attribution bias and regional variability limit standardised assessment. | Shows need for harmonised evaluation methods. |
| 8. Need for Standard KPIs | PMCs vary in reporting, completeness and risk prioritisation; proposed KPIs include completeness, signal timelines and follow-up compliance. | National KPIs needed for consistent performance tracking. |

7. Regulatory Evolution, Governance, and Future Directions

India’s progress toward risk-based pharmacovigilance (RBPV) depends heavily on the strength, clarity, and adaptability of its regulatory framework. While substantial advances have been made under CDSCO and PvPI, further evolution is necessary to align India’s systems with global best practices, enhance public health responsiveness, and prepare for emerging therapeutic and epidemiological challenges. This section examines the regulatory landscape, international harmonization prospects, and long-term strategic directions.

7.1. Current Regulatory Landscape and Need for Refinement

7.1.1. Analysis of Current Indian PV Guidelines and Their Alignment with RBPV Principles

India’s national pharmacovigilance regulations are grounded in Schedule Y of the Drugs and Cosmetics Rules, PvPI guidance documents, and CDSCO notifications [62, 63]. Over the past decade, CDSCO has strengthened requirements for spontaneous ADR reporting, Periodic Safety Update Reports (PSURs), post-marketing surveillance studies, causality assessment, and expedited reporting for serious adverse drug reactions. However, these regulations remain largely product-agnostic, applying uniform reporting expectations irrespective of risk category. Comparative analyses reveal that India’s framework, while aligned with WHO and ICH principles, still lacks formal, mandatory risk-based segmentation, unlike EMA’s GVP modules and FDA’s REMS frameworks [64, 65]. To operationalise RBPV at the national level, regulatory updates should mandate risk-prioritised pharmacovigilance planning for high-risk products, require targeted risk-minimisation strategies as part of marketing authorisation conditions, and integrate risk-classification criteria into expectations for ICSR triage.

7.1.2. The Role of CDSCO in Enforcing RBPV

CDSCO’s regulatory authority is central to India’s transition toward risk-based pharmacovigilance, with its expanding functions now encompassing the evaluation of signals submitted by PvPI, the conduct of benefit–risk assessments, the imposition of post-marketing commitments, and the issuance of safety communications and product recalls. For effective enforcement of RBPV, CDSCO must also formalise

risk-based inspection models for pharmaceutical companies, implement differentiated pharmacovigilance requirements based on therapeutic class and product risk, establish structured review processes for iRMPs and targeted safety studies, and ensure systematic monitoring of compliance with DHPC dissemination and controlled access programmes. Recent CDSCO actions such as mandating post-marketing studies for certain biosimilars and oncology drugs demonstrate movement toward RBPV-like regulatory expectations [66].

7.1.3. Proposed Policy Changes for Mandatory RMPs and REMS in India

Given India's high consumption of complex generics, biosimilars, and FDCs, experts increasingly advocate for:

- mandatory India-specific RMPs (iRMPs) for medium- and high-risk products
- conditional approvals tied to risk-minimization tools
- REMS-like programs for teratogenic, immunomodulatory, and narrow-therapeutic-index medicines
- mandatory registries for anti-TB, antiretroviral, oncology, and immunobiological products

Policy proposals presented in national PV workshops and scientific publications underscore the feasibility of embedding these frameworks within India's regulatory structure [67, 68].

7.2. International Harmonization and Collaboration

7.2.1. Aligning Indian RBPV Practices with WHO-UMC Standards

India's PvPI is recognized as a full member of the WHO Programme for International Drug Monitoring and contributes data to Vigibase. Alignment with WHO-UMC principles supports standardized MedDRA coding, adherence to Vigigrade completeness benchmarks, the use of harmonized signal-detection methodologies, and the international sharing of validated safety signals. Given India's large population and early adoption of generics, its data contribute significantly to global signal detection efforts [69]. Strengthening RBPV will amplify India's influence in international PV networks.

7.2.2. Data-Sharing Protocols and Global Signal Detection Networks

Global collaboration is critical for the early detection of rare or long-latency adverse events, and India already contributes through its participation in Vigibase, Uppsala Reports, WHO signal-review panels, and regional pharmacovigilance capacity-building networks. Looking ahead, the evolution of RBPV in India will require strengthened data-sharing protocols between CDSCO and the EMA, CDSCO and the US FDA, and broader cooperation between India and regulatory authorities across Southeast Asia. Such collaborations support shared risk evaluations, harmonized safety alerts, and aligned regulatory actions [70].

7.2.3. The Future of Reliance on Foreign Regulatory RMPs

India currently accepts foreign RMPs during regulatory submissions, especially for innovator molecules and biosimilars. However, reliance on foreign plans may overlook:

- India-specific epidemiology (e.g., tuberculosis prevalence)
- genetic polymorphisms altering risk profiles
- polypharmacy patterns unique to Indian clinical practice
- differences in healthcare accessibility and monitoring infrastructure

A future direction involves requiring adapted, localised RMP modules integrating Indian population risks, local utilization patterns, and context-specific risk-minimization tools [71].

7.3. Long-Term Vision for Pharmacovigilance in India

7.3.1. Integrating Patient-Centric PV and Personalized Medicine

The emerging paradigm of personalized medicine, driven by genomics, biomarkers and real-world data, necessitates pharmacovigilance systems capable of population stratification, genomic-risk-informed safety monitoring, pharmacogenomic tools for predicting adverse drug reactions, and the integration of patient-reported outcomes through digital interface. Indian genomics initiatives (e.g., GenomeIndia project) will enhance capacity for precision risk identification, aligning PV with personalized therapeutic strategies [72].

7.3.2. Strategies for Sustaining Digital Transformation

Long-term sustainability of digital RBPV requires:

- nationwide EHR interoperability standards
- cloud-based PV analytics platforms
- privacy-and-security-compliant data pipelines
- sustained investment in AI/ML R&D
- digital literacy training for healthcare providers

Integration with national digital health frameworks such as ABDM (Ayushman Bharat Digital Mission) will further enable scalable, data-driven RBPV [73, 74].

7.3.3. Preparing for Future Public Health Crises (e.g., Vaccine PV and Pandemic Preparedness)

The COVID-19 pandemic demonstrated the necessity of strong risk-based vaccine surveillance systems, making it essential for India to strengthen active surveillance platforms for vaccine-related adverse events, build rapid-cycle analysis capacity, expand genomic surveillance to assess variant-vaccine interactions, and enhance public communication systems to manage safety concerns and misinformation. Risk-based frameworks will be essential for emerging vaccines, novel therapeutics, and biologics used during future epidemics and pandemics [75, 76].

Table 3: Key Regulatory Updates Needed to Operationalise RBPV in India

| Regulatory Update | Description | Intended Impact |
|--|---|--|
| Risk-prioritised PV plans | Require MAHs to submit PV plans aligned with product risk (e.g., high-risk, high-use or vulnerable-population drugs). | Focuses surveillance on products with the greatest safety concerns. |
| Targeted risk-minimisation requirements | Include product-specific RMMs (iRMPs, DHPCs, CAPs, post-marketing studies) as conditions of approval. | Enhances prevention and mitigation of known or anticipated risks. |
| Risk-based ICSR triage standards | Integrate risk classification into national ADR reporting and triage processes. | Improves efficiency by accelerating review of high-priority and serious cases. |

8. Conclusion and Recommendations

India stands at a pivotal point in its pharmacovigilance evolution. With a rapidly expanding pharmaceutical market, complex therapeutic landscapes, and vast population heterogeneity, the adoption of risk-based pharmacovigilance (RBPV) is both an opportunity and a necessity. The preceding sections have illustrated how risk-stratified approaches can enhance efficiency, improve signal detection, enable

targeted safety actions, and strengthen public health protection. This concluding section synthesizes key findings and offers evidence-based recommendations for India's regulators, industry, healthcare providers, and academic institutions.

8.1. Synthesis of Findings

8.1.1. Summary of RBPV Benefits and Achieved Outcomes

The literature and national experience demonstrate that RBPV offers multiple advantages:

- Improved efficiency through reduced processing of low-value ICSRs and resource prioritization for high-risk products [44, 77].
- Earlier detection of important safety signals, supported by AI/ML-assisted triage and stratified data workflows [47, 78].
- Enhanced data completeness, with improved VigiGrade scores observed in centres applying structured templates [24, 46].
- More effective risk minimisation, including targeted DHPCs, controlled access programs, and India-specific risk management plans [36, 38, 79].
- Better public trust and communication, owing to transparent regulatory actions and strengthened patient-centric digital tools [80, 81].

Overall, RBPV has begun to shift India's PV ecosystem from reactive reporting to proactive, prioritised safety governance.

8.1.2. Recapitulation of Persistent Challenges

Despite progress, several systemic constraints remain:

- Variability in reporting quality and PMC performance
- Limited EHR integration and interoperability gaps
- Under-representation of private-sector and rural data
- Persistent under-reporting, especially for AYUSH and OTC products
- Lack of standardized national KPIs for RBPV outcome evaluation
- Insufficient workforce capacity in PV analytics and signal management

Addressing these limitations is essential to fully realizing the benefits of RBPV.

8.2. Actionable Recommendations for Stakeholders

8.2.1. Recommendations for Regulatory Bodies (CDSCO/PvPI)

1. Mandate India-specific RMPs (iRMPs) for medium- and high-risk medicines, including biosimilars, oncology products, and FDCs [52, 67].
2. Introduce formal RBPV guidelines, defining risk categories, required surveillance intensities, and reporting expectations.
3. Launch a risk-based inspection programme for MAH pharmacovigilance systems.
4. Implement national KPIs for data quality, signal timelines, and PMC performance [54, 69].
5. Strengthen digital PV infrastructure with interoperable EHR–PV data pipelines and AI-enabled triage tools [31, 78].
6. Expand PV mandates for AYUSH manufacturers and integrate AYUSH data streams with mainstream PV.

8.2.2. Recommendations for the Pharmaceutical Industry

1. Develop risk-prioritised PV plans aligned with ICH E2E and tailored to Indian epidemiology.

2. Implement AI/ML-based case prioritization and automated data mining [31].
3. Strengthen post-marketing studies and registries, especially for biosimilars and biologics.
4. Improve DHPC quality and bilingual dissemination, with effectiveness monitoring.
5. Support training and capacity-building initiatives in partnership with PvPI and academic institutions.

8.2.3. Recommendations for Healthcare Providers and Academia

1. Incorporate risk-based ADR reporting training into medical, pharmacy, and nursing curricula [35, 57].
2. Establish hospital-based multidisciplinary safety committees aligned with RBPV practices.
3. Expand research on population-specific ADR patterns, including pharmacogenomic studies [82].
4. Foster community engagement through public awareness programs and patient-centric reporting tools.
5. Promote collaborative research with regulators and industry to refine India-specific risk-minimisation strategies.

8.3. Final Perspective on India's Role in Global Pharmacovigilance

India's demographic scale, genetic diversity, and unique pharmaceutical landscape position it as a critical global contributor to drug safety science. As the world's largest supplier of generic medicines, India's PV data influence global benefit–risk evaluations. Strengthening RBPV will enable India to move from being a high-volume data contributor to a thought leader in risk-stratified medicine safety.

Looking ahead, India must:

- leverage national digital health infrastructure (ABDM),
- scale AI/ML-driven analytics,
- adopt personalized-medicine–aligned safety strategies, and
- modernize its regulatory framework with risk-based expectations.

If these priorities are addressed, India can become a regional and global exemplar of RBPV combining innovation, scalability, and public-health impact.

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