Review Article

Strategic Impact of ICH E2E Guidelines on Risk Management Planning (RMP) for New Drug Application

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ABSTRACT

Risk Management Planning (RMP) has become an essential component of lifecycle pharmacovigilance for newly approved medicines. Pre-approval clinical trials often provide limited safety information because of restricted sample size, short follow-up duration, and selective patient populations. The International Council for Harmonisation (ICH) E2E guideline provides a structured framework for pharmacovigilance planning through safety specification and pharmacovigilance plans. In India, the New Drugs and Clinical Trials Rules, 2019 and pharmacovigilance guidance for Marketing Authorization Holders provide the regulatory basis for post-marketing safety monitoring, including Periodic Safety Update Reports (PSURs) and Risk Management Plans wherever applicable. This review evaluates the strategic impact of ICH E2E principles on Indian regulatory expectations for RMPs in new drug applications. The study highlights the relationship between safety specification, pharmacovigilance planning, PSUR obligations, and lifecycle benefit–risk assessment. The review also identifies current gaps in Indian implementation, including limited standardization, lack of explicit triggers for mandatory RMP submission, and insufficient integration of local real-world evidence. Finally, policy recommendations are proposed to strengthen Indian pharmacovigilance systems and improve long-term patient safety.

Keywords: ICH E2E; Risk Management Plan; Pharmacovigilance; CDSCO; New Drugs and Clinical Trials Rules 2019; Marketing Authorization Holder; PSUR; India; Patient Safety.

INTRODUCTION

New drug approval is not the end of safety evaluation because pre-approval clinical trials may not fully detect rare, delayed, or population-specific adverse drug reactions. Therefore, structured post-marketing pharmacovigilance and Risk Management Planning are essential for long-term patient safety. ICH E2E provides a framework for pharmacovigilance planning through two major elements: Safety Specification and Pharmacovigilance Plan, especially for the early post-marketing period of a new drug.[1,2]

In India, the New Drugs and Clinical Trials Rules, 2019 provide the legal framework for new drug approval and post-marketing safety obligations. These rules include requirements for Periodic Safety Update Reports (PSURs), including signal and risk evaluation, benefit–risk assessment, and Risk Management Plan details where applicable.[3,4]

The Pharmacovigilance Guidance Document for Marketing Authorization Holders, prepared by the Indian Pharmacopoeia Commission (IPC) in collaboration with the Central Drugs Standard Control Organisation (CDSCO), further defines the responsibilities of Marketing Authorization Holders for pharmacovigilance activities in India.[5]

Thus, integration of ICH E2E principles into Indian Risk Management Planning can strengthen proactive identification, monitoring, and mitigation of safety risks after new drug approval. This review discusses how ICH E2E safety specification and pharmacovigilance planning concepts are reflected in Indian regulatory expectations and how they can improve lifecycle benefit–risk management and patient safety.

2. NEED FOR RISK MANAGEMENT PLANNING IN NEW DRUG APPROVAL

Risk Management Planning is essential in new drug approval because the safety profile of a medicine is not completely known at the time of marketing authorization. Pre-approval clinical trials are usually conducted in controlled conditions with limited sample size, selected patient populations, and relatively short duration. Therefore, rare adverse drug reactions, delayed toxicities, drug interactions, medication errors, and safety issues in special populations may become evident only after wider use in the real-world population.[6,7]

ICH E2E recognizes this limitation and provides guidance for pharmacovigilance planning, especially for the early post-marketing period of a new drug. The guideline focuses on two major components: Safety Specification and Pharmacovigilance Plan, which may be submitted at the time of licence application. These components help identify important identified risks, important potential risks, and missing information before the drug is used in a larger population.[1,8]

In the Indian regulatory context, Risk Management Planning is important because the New Drugs and Clinical Trials Rules, 2019 require post-marketing safety monitoring through mechanisms such as PSURs. These reports include signal and risk evaluation, benefit–risk assessment, and Risk Management Plan details where applicable.[3,4]

Risk Management Planning also strengthens the responsibilities of Marketing Authorization Holders by requiring continuous monitoring, documentation, and evaluation of safety concerns after approval. The IPC/CDSCO Pharmacovigilance Guidance Document for Marketing Authorization Holders describes pharmacovigilance responsibilities in India and aligns these activities with the Drugs and Cosmetics Act, Rules, and NDCT Rules, 2019.[5,9]

Therefore, Risk Management Planning supports a proactive approach to drug safety. It helps regulators and Marketing Authorization Holders identify risks early, plan suitable pharmacovigilance activities, implement risk-minimization measures, and maintain a favorable benefit–risk balance throughout the product lifecycle. This ultimately contributes to improved patient safety and better regulatory decision-making in new drug approval.[10]

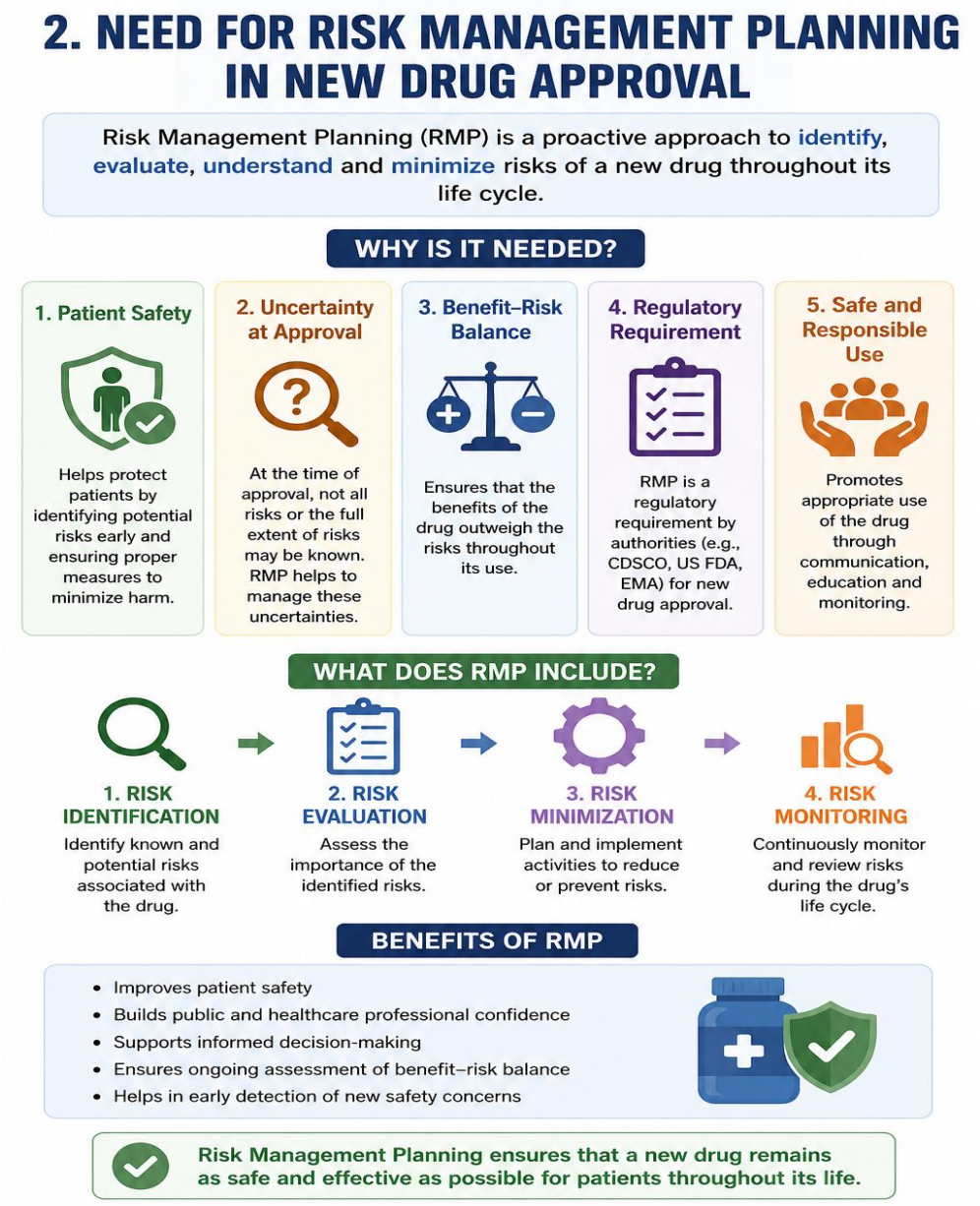

Figure 1: Need for Risk Management Planning in New Drug Applications [1]

3. OVERVIEW OF ICH E2E PHARMACOVIGILANCE PLANNING

The ICH E2E guideline, titled *Pharmacovigilance Planning*, provides guidance for planning pharmacovigilance activities, particularly before and during the early post-marketing period of a new drug. It applies to chemical entities, biotechnology-derived products, and vaccines. The main aim of the guideline is to help sponsors and regulators identify important safety concerns and plan suitable post-approval monitoring activities.[1,11]

The guideline mainly focuses on two key components: Safety Specification and Pharmacovigilance Plan. These components may be submitted at the time of licence application and may also be incorporated into the Common

Technical Document, depending on regional regulatory requirements.[1,23]

The Safety Specification summarizes the important safety concerns related to a drug. It includes important identified risks, important potential risks, and important missing information. It also considers populations or situations in which the drug may be used after approval but has not been adequately studied during pre-approval clinical trials.[12,13]

The Pharmacovigilance Plan describes how the identified safety concerns will be monitored and further evaluated after approval. For products with important identified risks, important potential risks, or missing information, additional pharmacovigilance activities may be required. For products without special safety concerns, routine pharmacovigilance may be sufficient.[14,24]

ICH E2E is important in new drug approval because it links pre-approval safety information with post-marketing safety surveillance. It supports a proactive approach to lifecycle safety monitoring, helps maintain a favorable benefit–risk balance, and provides a scientific basis for Risk Management Planning in regulatory submissions.[1,22]

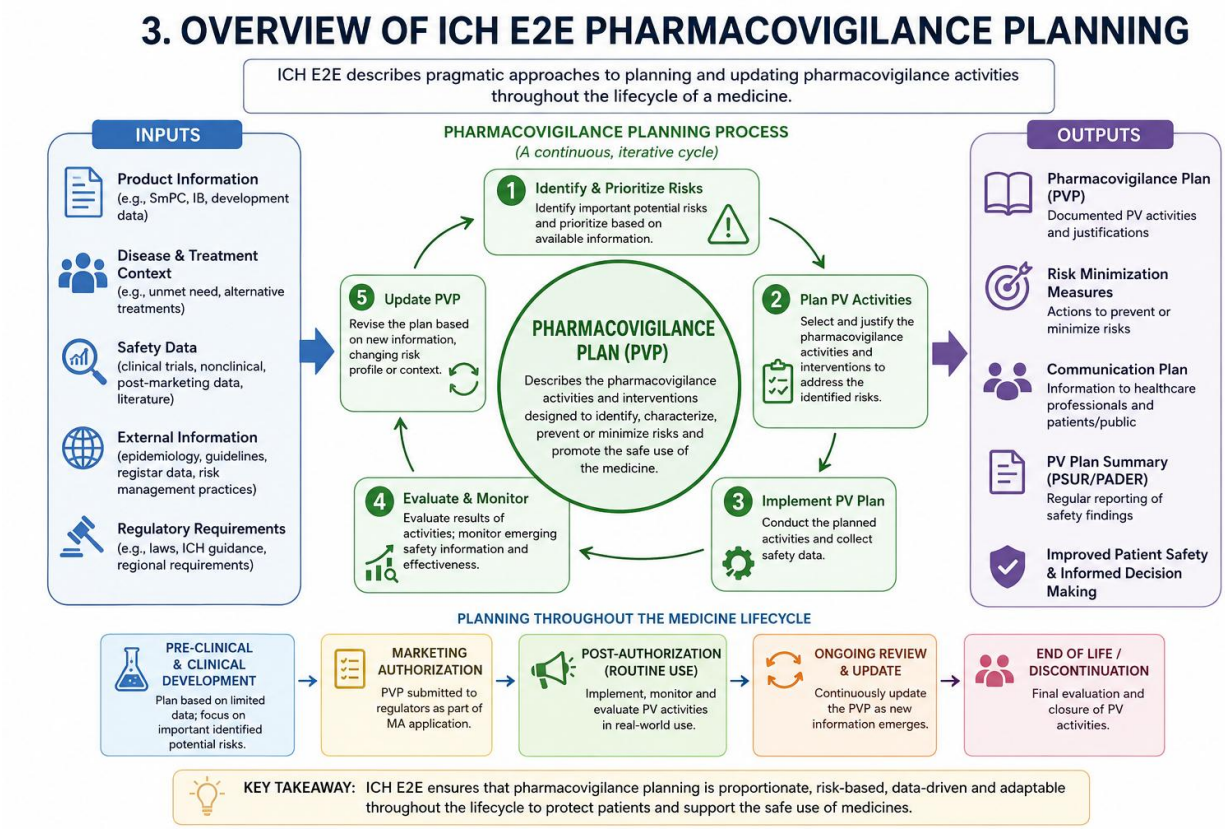

Figure 2: Overview of ICH E2E Pharmacovigilance Planning [7]

4. SAFETY SPECIFICATION UNDER ICH E2E

The Safety Specification is a key component of ICH E2E pharmacovigilance planning. It provides a structured summary of the important safety concerns related to a medicinal product based on available non-clinical, clinical, and post-marketing data. Its main purpose is to identify what is already known, what is suspected, and what information is still missing about the drug's safety profile.[1,12]

Under ICH E2E, the Safety Specification mainly includes important identified risks, important potential risks, and important missing information. It also considers safety concerns in populations not adequately studied during clinical development, such as pediatric patients, geriatric patients, pregnant women, lactating women, and patients with renal or hepatic impairment.[13,15]

This section is important for Risk Management Planning because it forms the basis for the Pharmacovigilance Plan. By identifying key safety concerns early, regulators and Marketing Authorization Holders can plan appropriate post-marketing monitoring, signal detection, additional safety studies, and risk-minimization activities.[16,20]

5. PHARMACOVIGILANCE PLAN UNDER ICH E2E

Under ICH E2E, the Pharmacovigilance Plan explains how the important safety concerns identified in the Safety Specification will be monitored after approval. Its purpose is to define whether routine pharmacovigilance is sufficient or whether additional pharmacovigilance activities are needed for products with important identified risks, important potential risks, or important missing information.[1,23]

The guideline indicates that routine pharmacovigilance may be enough for products without special safety concerns, while products with significant safety issues may require extra measures. These additional activities can include targeted follow-up, observational studies, registries, or other methods designed to better characterize risks, address gaps in knowledge, and support ongoing benefit–risk evaluation.[14,24]

ICH E2E treats the Pharmacovigilance Plan as part of lifecycle safety monitoring. It recommends early involvement of pharmacovigilance experts and early dialogue with regulators, and notes that the plan can be revised as new safety information emerges after marketing. In this way, the Pharmacovigilance Plan helps convert pre-approval safety findings into a structured post-marketing strategy for continuous monitoring and patient protection.[21,22]

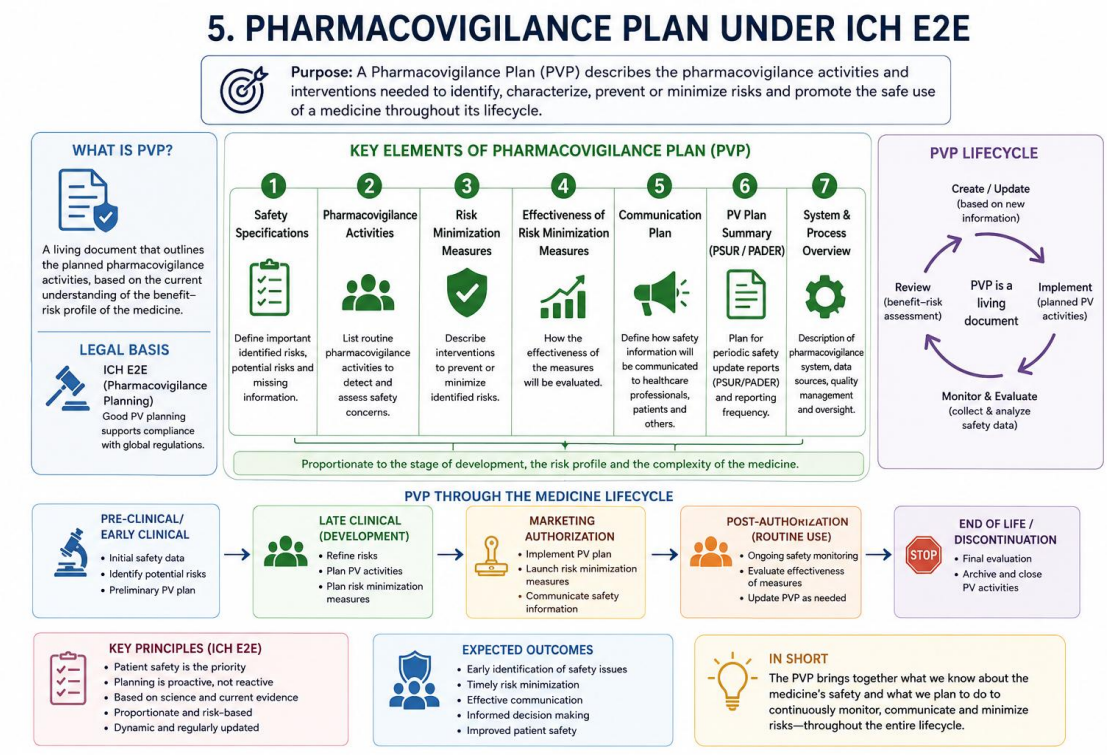

Figure 3: Pharmacovigilance Plan under ICH E2E [10]

6. INDIAN REGULATORY FRAMEWORK: CDSCO AND NDCT RULES, 2019

In India, the Central Drugs Standard Control Organisation (CDSCO) functions under the Ministry of Health and Family Welfare and is the national regulatory authority for drugs. The New Drugs and Clinical Trials Rules, 2019 provide the main legal framework for regulation of new drugs, investigational new drugs, clinical trials, bioavailability and bioequivalence studies, and Ethics Committees.[3,4]

The NDCT Rules also emphasize post-marketing safety oversight. They state that, after approval, a new drug should be closely monitored because clinical trial data are limited and real-world use may reveal uncommon risks. The Rules require applicants who import or manufacture a new drug for sale or distribution to maintain a pharmacovigilance system for collecting, processing, and forwarding adverse drug reaction reports.[5,25]

For post-marketing surveillance, the NDCT Rules require submission of PSURs every six months for the first two years after approval and annually for the next two years, unless extended in the interest of public health. The PSUR format includes signal and risk evaluation, details of the Risk Management Plan, actions taken to mitigate safety concerns, and overall safety and benefit–risk evaluation.[3,45]

7. RMP AND PSUR EXPECTATIONS IN INDIA

In India, PSURs are a key post-marketing requirement for new drugs. Under the NDCT Rules, 2019, PSURs are to be submitted every six months for the first two years after approval and annually for the next two years unless the Central Licensing Authority extends the reporting period in the interest of public health.[3,35]

The Indian framework also links PSURs with Risk Management Planning. The NDCT Rules specify that PSURs should include signal and risk evaluation, details of the Risk Management Plan in place, brief details of safety concerns and actions taken to mitigate them, and an overall safety and benefit–risk evaluation.[3,6]

The current IPC/CDSCO Pharmacovigilance Guidance Document for Marketing Authorization Holders reinforces this approach. It states that the guidance covers the preparation and submission of PSURs and the submission of

a Risk Management Plan wherever applicable as part of broader pharmacovigilance responsibilities.[5,26]

Therefore, Indian regulatory expectations treat PSURs as the core post-marketing safety reporting tool, while RMP elements are incorporated where applicable to support continuous monitoring, risk evaluation, and benefit–risk assessment throughout the product lifecycle.[27,28]

8. MAPPING ICH E2E PRINCIPLES WITH INDIAN RMP REQUIREMENTS

Indian RMP expectations are aligned with, but not identical to, ICH E2E. ICH E2E structures pharmacovigilance planning around the Safety Specification and Pharmacovigilance Plan, including important identified risks, important potential risks, and important missing information.[1,23]

In India, the NDCT Rules, 2019 require PSURs to include signal and risk evaluation and details of the Risk Management Plan, while the IPC/CDSCO guidance states that RMP submission applies wherever applicable.[3,5]

The alignment is strongest in the treatment of safety concerns. Indian guidance states that overall safety evaluation should include important identified risks, important potential risks, and important missing information, which closely reflects the ICH E2E safety specification model.[5,24]

The guidance also states that the RMP is a dynamic, stand-alone document that should be updated throughout the product life cycle, showing consistency with ICH E2E's lifecycle approach to pharmacovigilance planning.[20,30]

9. STRATEGIC IMPACT ON NEW DRUG APPROVAL AND PATIENT SAFETY

The integration of ICH E2E principles into Indian risk management practice can strengthen new drug approval by converting limited pre-approval safety data into a structured plan for post-marketing monitoring.[1,21]

ICH E2E is specifically intended to support pharmacovigilance planning for the early post-marketing period, with emphasis on a Safety Specification and Pharmacovigilance Plan, and it recommends that pharmacovigilance activities continue throughout the product life cycle.[1,22]

In the Indian context, this approach has strategic value because the NDCT Rules, 2019 require PSURs to include signal and risk evaluation, details of the Risk Management Plan in place, and an overall safety and benefit–risk evaluation.[3,45]

The IPC/CDSCO guidance further states that the aim of an RMP is to identify, characterize, and minimize important risks and that the RMP should be updated throughout the product life cycle.[5,26]

Therefore, the strategic impact of ICH E2E on Indian new drug approval lies in promoting earlier identification of safety concerns, structured post-marketing surveillance, continuous benefit–risk reassessment, and timely risk-minimization actions, all of which can improve regulatory decision-making and long-term patient safety.[24,29]

10. CURRENT GAPS IN INDIAN RMP IMPLEMENTATION

Several implementation gaps remain in India's Risk Management Planning framework.[25,27]

First, the regulatory trigger for RMP submission is still not fully explicit. The NDCT Rules, 2019 refer to PSUR inclusion of details of the Risk Management Plan "if any," and the IPC/CDSCO guidance describes RMP submission as applicable "wherever applicable." This wording supports a risk-based approach but also creates uncertainty regarding when an RMP becomes mandatory.[3,5]

Second, India appears to have limited standardization and public transparency for RMPs. Existing rules discuss RMP content and submission but do not establish a public-facing system comparable to international agencies such as the European Medicines Agency.[7,44]

Third, although Indian guidance recognizes that the RMP should be a dynamic, stand-alone document, clearer operational expectations are still needed for updating RMPs, linking them with PSUR findings, and documenting the effectiveness of risk-minimization measures.[20,30]

Finally, Indian implementation would benefit from stronger use of local real-world safety data, including national pharmacovigilance outputs, in routine RMP revision and benefit–risk reassessment.[26,38]

11. POLICY RECOMMENDATIONS

India should adopt a clear trigger-based policy for mandatory RMP submission in selected categories of new drugs, such as products with novel mechanisms, limited pre-approval safety data, serious safety concerns, or use in vulnerable populations.[25,27]

A standard Indian RMP template should be issued, explicitly structured around the core ICH E2E elements: important identified risks, important potential risks, missing information, and a pharmacovigilance plan.[1,23]

India should also require that the RMP be updated across the product life cycle and formally linked with PSUR findings, signal evaluation, and risk-mitigation actions.[20,35]

Another priority is to strengthen evaluation of risk-minimization effectiveness. International risk-management guidance emphasizes that RMPs should not only describe risks but also document the systems needed to identify, characterize, and minimize important risks while maintaining a favorable benefit–risk balance.[7,24]

Finally, India should improve transparency and use of local data by encouraging publication of non-confidential RMP summaries and integrating Indian real-world pharmacovigilance data more systematically into RMP updates.[38,44]

Table 1: Current Gaps in Indian RMP (Risk Management Plan) Implementation

Sr. No.	Current Gap in Indian RMP Implementation	Description	Impact on Pharmacovigilance/System	Suggested Improvement
1	Lack of Comprehensive RMP Guidelines	India has limited harmonized guidance compared with ICH E2E/EU-GVP requirements.	Inconsistent RMP preparation and implementation across companies.	Develop detailed CDSCO-aligned national RMP guidance harmonized with ICH standards
2	Limited Mandatory Requirement	RMP submission is not uniformly mandatory for all products.	Variable adoption of proactive risk management practices.	Make RMP compulsory for selected high-risk and new products.
3	Inadequate Post-Marketing Surveillance	Weak active surveillance and limited real-world evidence generation.	Delayed detection of safety signals and adverse reactions.	Strengthen post-marketing studies and active surveillance systems.
4	Underreporting of Adverse Drug Reactions (ADRs)	Low awareness and participation among healthcare professionals and patients.	Reduced quality of safety database and signal detection.	Increase ADR awareness programs and simplify reporting systems.
5	Limited Pharmacovigilance Infrastructure	Uneven availability of trained PV personnel and digital systems across organizations.	Poor monitoring and delayed safety evaluation.	Improve PV infrastructure and workforce training.
6	Lack of Risk Minimization Evaluation	Effectiveness of risk minimization measures is rarely assessed systematically.	Uncertain impact of safety interventions.	Introduce mandatory effectiveness assessment methodologies.
7	Poor Integration of Real-World Data	Limited utilization of electronic health records, registries, and databases.	Insufficient evidence for long-term safety evaluation.	Promote use of real-world evidence and healthcare databases.
8	Inconsistent Periodic Safety Reporting	Variability in PSUR/PBRER quality and timelines.	Difficulty in continuous benefit-risk assessment.	Standardize reporting formats and strengthen regulatory review.
9	Limited Stakeholder Awareness	Healthcare professionals often have inadequate understanding of RMP concepts.	Weak implementation of risk minimization activities.	Conduct regular training and continuing medical education programs.
10	Regulatory Resource Constraints	Limited manpower and expertise within regulatory authorities.	Delays in review, monitoring, and signal management.	Enhance regulatory capacity and technical expertise.
11	Weak Communication Strategies	Safety communication to patients and healthcare professionals is insufficient.	Poor awareness of emerging risks and precautions.	Develop structured safety communication frameworks.
12	Lack of Continuous RMP Updating	RMPs may not be revised regularly according to emerging safety data.	Outdated risk profiles and inadequate mitigation strategies.	Ensure lifecycle-based dynamic updating of RMPs.

CONCLUSION

ICH E2E provides a strong scientific basis for structured pharmacovigilance planning through the concepts of Safety Specification and Pharmacovigilance Plan. These principles are highly relevant to Indian new drug approval because they support early identification of important safety concerns, continuous post-marketing monitoring, and lifecycle benefit–risk assessment.[1,7]

In India, the NDCT Rules, 2019 and the IPC/CDSCO pharmacovigilance guidance for Marketing Authorization Holders show alignment with this approach through requirements for PSUR submission, signal and risk evaluation, benefit–risk assessment, and RMP-related information where applicable.[3,5]

However, clearer criteria for mandatory RMP submission, stronger standardization of RMP format, better linkage between RMPs and PSUR findings, and greater use of Indian real-world safety data are still needed.[25,27]

Overall, better integration of ICH E2E principles into Indian regulatory practice can strengthen post-marketing safety surveillance, improve regulatory decision-making, and enhance long-term patient safety for newly approved drugs.[24,30]

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REFERENCES

1. International Council for Harmonisation (ICH). ICH Harmonised Tripartite Guideline E2E: Pharmacovigilance Planning. Geneva: ICH; 2004.
2. CIOMS Working Group. Management of Safety Information from Clinical Trials. Geneva: CIOMS; 2005.
3. Government of India. New Drugs and Clinical Trials Rules, 2019. Ministry of Health and Family Welfare; 2019.
4. Drugs and Cosmetics Act and Rules. New Delhi: Government of India.
5. Indian Pharmacopoeia Commission. Pharmacovigilance Guidance Document for Marketing Authorization Holders. Ghaziabad: IPC.
6. Central Drugs Standard Control Organisation (CDSCO). Guidance for Industry on Pharmacovigilance Requirements. New Delhi: CDSCO.
7. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk Management Systems. Amsterdam: EMA.
8. World Health Organization. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Geneva: WHO.
9. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255-1259.
10. Strom BL, Kimmel SE, Hennessy S. Pharmacoepidemiology. 5th ed. Chichester: Wiley-Blackwell; 2012.
11. Waller P. An Introduction to Pharmacovigilance. 2nd ed. London: Wiley; 2017.
12. Meyboom RH, Egberts AC, Edwards IR, Hekster YA, de Koning FH, Gribnau FW. Principles of signal detection in pharmacovigilance. Drug Saf. 1997;16(6):355-365.
13. Hartigan-Go K. Pharmacovigilance and drug safety in clinical trials. Drug Saf. 2000;22(6):423-426.
14. Council for International Organizations of Medical Sciences. Practical Aspects of Signal Detection in Pharmacovigilance. Geneva: CIOMS; 2010.
15. Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? Lancet. 1995;345:807-808.
16. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. JAMA. 1998;279(15):1200-1205.
17. Uppsala Monitoring Centre. The Importance of Pharmacovigilance. UMC Publications; 2002.
18. Gupta SK. Pharmacology and Therapeutics in India: Current Perspectives. New Delhi: Jaypee Brothers; 2011.
19. World Health Organization. WHO Pharmacovigilance Indicators: A Practical Manual for Assessment of Pharmacovigilance Systems. Geneva: WHO; 2015.
20. European Medicines Agency. Risk Management Plan Guidance for Medicinal Products. EMA Publications.
21. Breckenridge A, Woods K, Walley T. Pharmacovigilance and regulation. BMJ. 2005;331:949-950.
22. Mann RD, Andrews EB. Pharmacovigilance. 2nd ed. Chichester: Wiley; 2007.
23. ICH Secretariat. Integrated Addendum to ICH E2C(R2): Periodic Benefit-Risk Evaluation Report. Geneva: ICH.
24. Arlett P, et al. Proactive pharmacovigilance planning and risk minimization. Drug Saf. 2012;35(9):695-705.
25. Banerjee AK. Pharmacovigilance in India: Current status and future challenges. Int J Risk Saf Med. 2013;25(3):123-129.
26. Biswas P. Pharmacovigilance in Asia. J Pharmacol Pharmacother. 2013;4(Suppl1):S7-S19.
27. Gupta YK, Nayak RP. Pharmacovigilance in India: Present scenario and future challenges. Drug Saf. 2014;37(7):543-547.
28. Singh GN, et al. Pharmacovigilance in India. Indian J Pharmacol. 2011;43(6):629-632.
29. World Health Organization. The Safety of Medicines in Public Health Programmes. Geneva: WHO; 2006.
30. EMA. Good Pharmacovigilance Practices: Module IX Signal Management. Amsterdam: EMA.
31. FDA. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Silver Spring: US FDA.
32. US FDA. Best Practices in Drug Risk Management and Communication. Silver Spring: FDA.
33. ICH. E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Geneva: ICH.
34. ICH. E2D Post-Approval Safety Data Management. Geneva: ICH.
35. ICH. E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. Geneva: ICH.
36. ICH. E2F Development Safety Update Report. Geneva: ICH.
37. EMA. Guideline on Safety Specification and Pharmacovigilance Planning. London: EMA.
38. Pharmacovigilance Programme of India (PvPI). National Coordination Centre Publications. Ghaziabad: IPC.
39. World Health Organization. International Drug Monitoring: The Role of National Centres. Geneva: WHO.
40. Edwards IR. The WHO World Alliance for Patient Safety. Drug Saf. 2005;28(5):379-386.
41. Talbot J, Aronson JK. Stephens' Detection and Evaluation of Adverse Drug Reactions. 6th ed. Wiley-Blackwell.
42. Coulter DM. The New Zealand Intensive Medicines Monitoring Programme. Drug Saf. 2000;23(1):79-90.
43. ICH Official Website. International Council for Harmonisation Guidelines. Geneva: ICH.
44. EMA. European Union Risk Management Plan Format. EMA Publications.
45. CDSCO. Guidance on Submission of PSURs in India. New Delhi: CDSCO.
46. PvPI. National Pharmacovigilance Protocol of India. IPC Publications.
47. WHO Collaborating Centre for International Drug Monitoring. Signal Detection in Pharmacovigilance. UMC.
48. Pirmohamed M, et al. Adverse drug reactions as cause of admission to hospital. BMJ. 2004;329:15-19.
49. Classen DC, et al. Adverse drug events in hospitalized patients. JAMA. 1997;277(4):301-306.
50. Aronson JK. Meyler's Side Effects of Drugs. 16th ed. Elsevier; 2016.