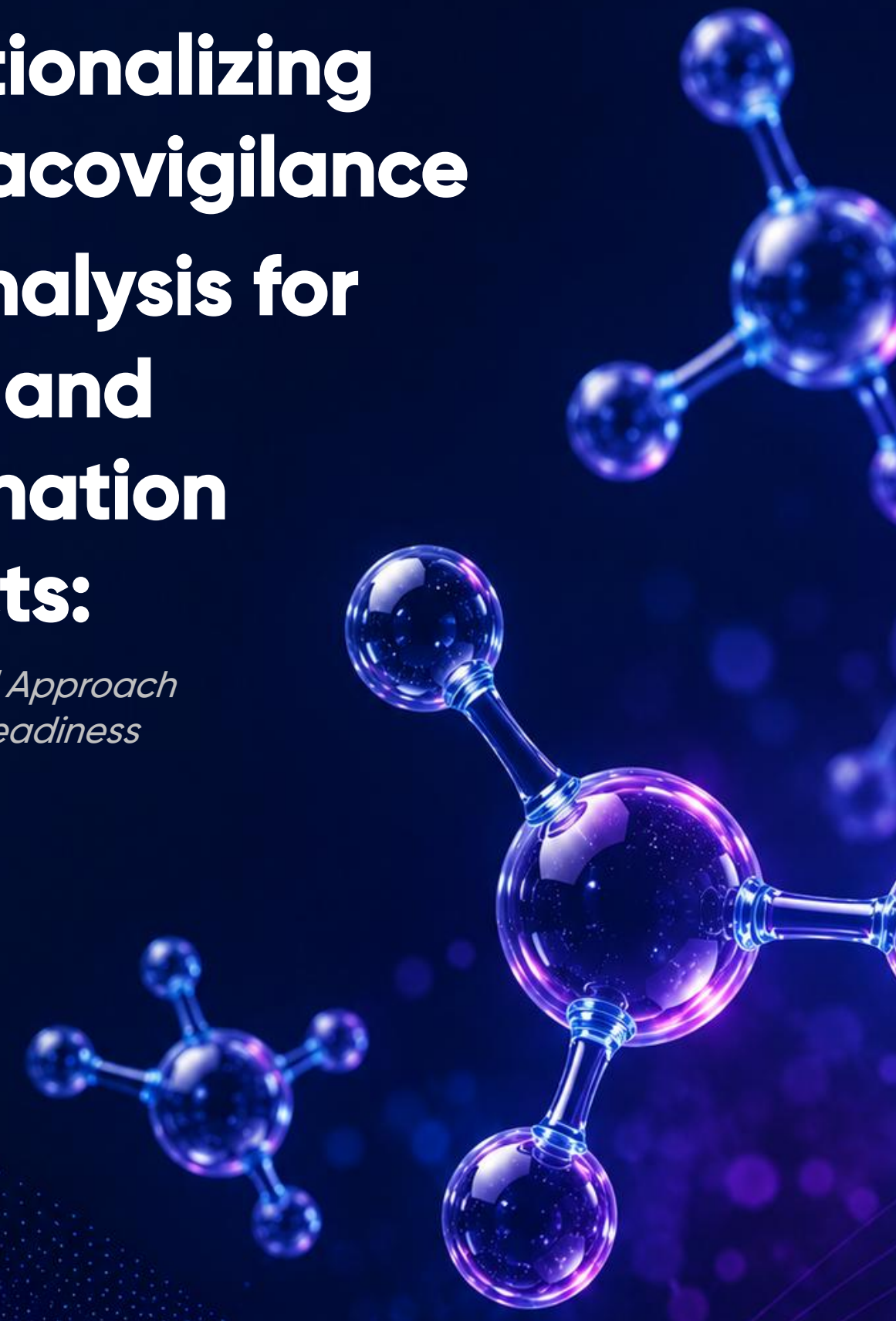
GOD® RESEARCH

Operationalizing Pharmacovigilance Gap Analysis for ATMPs and Combination Products:

A System-Level Approach to Inspection Readiness



Introduction

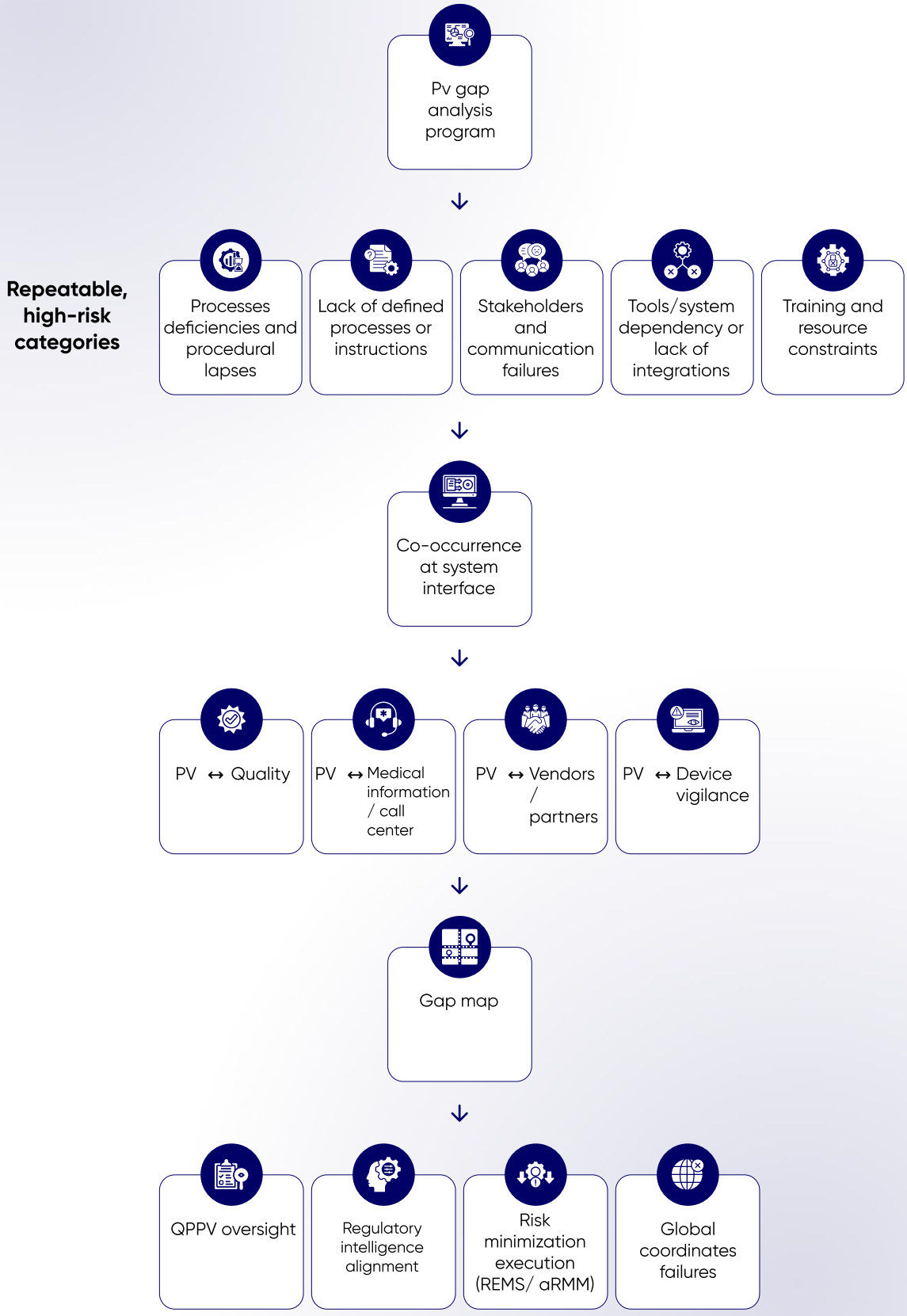
- The regulatory expectations for pharmacovigilance systems have evolved significantly with the emergence of ATMPs and combination products. Traditional PV systems were designed for chemically synthesized products with relatively linear safety profiles. In contrast, ATMPs require long-term follow-up, traceability, and integration with clinical and registry data, while combination products introduce overlapping obligations between drug safety and medical device vigilance.

- Regulators have responded accordingly. Under 21 CFR 314.80 and 600.80, the FDA requires robust post marketing safety reporting systems capable of timely detection, assessment, and reporting of adverse events. For combination products, 21 CFR Part 4 further mandates alignment between drug and device reporting requirements. Similarly, the MHRA, through UK Good Pharmacovigilance Practices (GVP), requires MAHs to maintain an integrated PV system supported by a functioning PSMF, effective QPPV oversight, and demonstrable inspection readiness.

- Despite the clearly defined expectations, inspection findings across both jurisdictions consistently highlight systemic failures at functional interfaces rather than isolated procedural gaps.

Evidence-Based Gap Patterns from PV Gap Analysis Programs

- Gap distribution patterns indicate a disproportionate concentration of deficiencies at cross-functional interfaces, reinforcing that system integration — not standalone process compliance — is the primary determinant of inspection readiness.

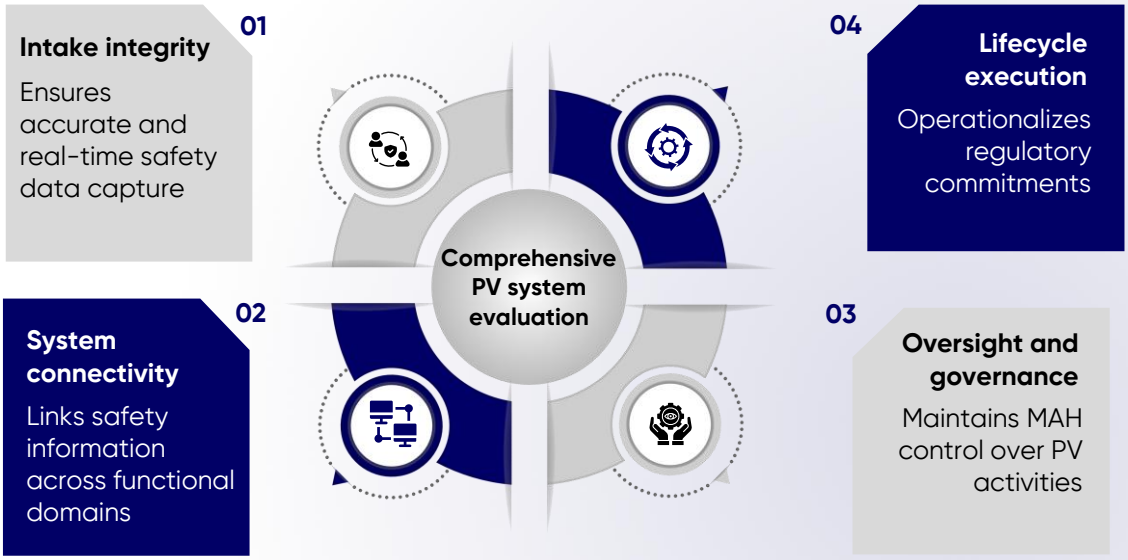

Pv gap analysis program
Repeatable, high-risk categories
Processes deficiencies and procedural lapses
Lack of defined processes or instructions
Stakeholders and communication failures
Tools/system dependency or lack of integrations
Training and resource constraints
Co-occurrence at system interface
PV ↔ Quality
PV ↔ Medical information / call center
PV ↔ Vendors / partners
PV ↔ Device vigilance
Gap map
QPPV oversight
Regulatory intelligence alignment
Risk minimization execution (REMS/ aRMM)
Global coordinates failures

Reframing the Problem: From Compliance to System Behaviour

- A recurring observation from inspections is that organizations often maintain extensive SOP frameworks and validated systems, yet fail to demonstrate control over how safety information flows across the organization.
- For example, adverse events may be correctly processed within a safety database, while product quality complaints are managed within a quality system, and device malfunctions are handled separately. However, the absence of structured linkage between these domains results in missing complete assessment, missed signals and delayed reporting. This directly conflicts with regulatory expectations for comprehensive safety evaluation under both FDA and MHRA frameworks.
- Similarly, safety-relevant information captured through Medical Information contact centres, Patient Support Programs, or third-party vendors is frequently not integrated into the PV system in a timely or consistent manner. Under 21 CFR 314.80(b), the FDA explicitly requires applicants to establish systems for the receipt, evaluation, and reporting of adverse experiences from all sources. MHRA and EU expectations under GVP Module VI extend this requirement to all organized data collection systems, including non-traditional channels.
- These gaps indicate that the core issue is not the absence of compliance structures, but the lack of system-level integration and control.

A Four-Layer Model for PV Gap Analysis

- To address this, Gap Analysis must move beyond document review and instead evaluate how the PV system performs across four interconnected control layers.



- This framework illustrates that pharmacovigilance compliance is evaluated not as isolated activities, but as an interconnected control system spanning intake, connectivity, oversight, and lifecycle execution. Consistent with FDA, ICH, and MHRA expectations, inspection risk often arises not from absence of procedures, but from breakdowns in operational linkage, governance, or execution across these layers.

Application to ATMPs and Combination Products

- The importance of this model becomes more pronounced when applied to ATMPs and combination products.

- For ATMPs, long-term follow-up obligations and traceability requirements demand continuous data integration over extended periods. However, many organizations lack mechanisms to reconcile data across clinical studies, registries, and post marketing surveillance systems, leading to fragmented safety oversight.

- For combination products, the coexistence of drug and device regulatory frameworks introduces ambiguity in event classification and reporting responsibilities. Under FDA requirements, a single event may trigger both adverse event reporting and medical device reporting obligations. Without a unified assessment framework, organizations risk under-reporting or misclassification, both of which are inspection-critical issues.

Operationalizing Gap Analysis: A Practical Approach

- Effective gap analysis requires testing the system under real conditions rather than relying solely on documentation review. One of the most effective approaches is end-to-end case tracing, where actual safety cases are followed from initial intake through reporting and signal evaluation. This method reveals breakdowns in data flow, classification, and decision-making that are not visible through SOP review alone.

- In parallel, interface testing between key functions, such as medical information, quality, and pharmacovigilance, helps identify disconnects in responsibilities and data exchange. Reconciliation exercises across safety databases, complaint systems, and partner data further expose inconsistencies that indicate lack of system control.

- This approach aligns with the practical gap analysis methodology outlined in your slide framework, particularly the emphasis on SME-led assessment, document analysis, and impact evaluation of identified gaps.

Conclusion

- Inspection readiness in modern pharmacovigilance systems is no longer defined by the presence of compliant procedures, but by the ability to demonstrate integrated system performance and control. ATMPs and combination products amplify this requirement by introducing long-term, cross-functional, and multi-regulatory complexities.

- The four-layer Gap Analysis model presented in this paper provides a structured, system-focused approach to identifying and addressing these challenges. By evaluating intake integrity, system connectivity, governance, and lifecycle execution, organizations can move beyond superficial compliance and build pharmacovigilance systems that are resilient, integrated, and inspection-ready.

References

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Author: Mohit Kapoor, Associate VP- Operations, Strategy and PM (Patient Safety)
cod-research.com | bd@cod-research.com