



Original Article

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Pharmacovigilance Should Separate Signal Strength from Clinical Actionability

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ABSTRACT

Pharmacovigilance often treats a statistically prominent drug–event association as if it were inherently closer to clinical or regulatory action. That inference is unsafe. Disproportionality, machine-learning prioritisation, longitudinal healthcare data, case-level assessment, and other signal methods answer questions about whether an association is unusual, reproducible, temporally coherent, or evidentially credible. They do not by themselves determine whether an intervention is warranted. Actionability additionally depends on the seriousness, magnitude, reversibility and preventability of harm; background risk; exposed-population vulnerability; therapeutic alternatives; time sensitivity; and the feasibility and consequences of intervention. This Current Opinion argues for an explicit separation between signal strength and clinical actionability. Statistical strength should describe the credibility and maturity of the safety association, whereas actionability should describe the consequence-sensitive case for doing something under current uncertainty. The distinction explains two recurrent pharmacovigilance problems: strong signals that remain insufficiently decision-ready and modest signals for which proportionate early action may nevertheless be justified. The proposed separation is a conceptual framework, not a validated scoring system, causal algorithm, or regulatory rule.

Keywords: *Pharmacovigilance, Signal detection, Disproportionality analysis, Clinical actionability, Causal inference, Risk minimisation*

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INTRODUCTION

Pharmacovigilance has become increasingly capable of finding statistical irregularities, but detection capacity can create an interpretive shortcut: the stronger the signal appears analytically, the more actionable it is presumed to be. That shortcut conflates two questions. A disproportionality analysis asks whether a drug–event pair is reported more often than expected relative to an internal comparator; it does not establish incidence, attributable risk, or causality. READUS-PV was developed precisely because design and reporting choices materially affect how such analyses can be interpreted [1]. Meta-research has also shown that published disproportionality studies use validity-enhancing strategies inconsistently, including sensitivity analyses, external contextualisation, and complementary evidence [2].

The evidential landscape is broader than spontaneous reports. Routinely collected health data can inform signal validation and prioritisation when the underlying clinical question, exposure definition, outcome ascertainment, comparator, and confounding structure are suitable. In the EHDEN network feasibility study, such analyses

informed several signal decisions but did not resolve every case, illustrating both their value and their limits [3]. Regulatory practice likewise separates detection from downstream assessment. European signal management encompasses validation, confirmation, analysis, prioritisation, recommendation, and possible regulatory action rather than treating a statistical alert as the action itself [4]. In the United States, a longitudinal assessment of safety-related labelling changes found heterogeneous triggering and supporting evidence sources rather than a single dominant path from spontaneous reporting to label revision [5]. Real-world data, electronic health records, digital data, and spontaneous reports therefore enlarge the evidence base, but they are complementary rather than interchangeable [6].

This article argues that pharmacovigilance should make this separation explicit. “Signal strength” is used here for the credibility and maturity of the evidence supporting a suspected medicine–event association. “Clinical actionability” is used for the consequence-sensitive case for intervening, communicating, investigating, restricting, monitoring, or otherwise changing practice under present uncertainty. The distinction is proposed rather than empirically validated. It is intended to prevent statistical prominence from silently absorbing questions about harm severity, preventability, patient vulnerability, exposure, alternatives, and urgency that belong to a different decision domain.

Statistical signal strength

Statistical signal strength begins with what a detection method actually measures. Disproportionality estimates are properties of reporting distributions, not direct estimates of clinical risk. Their magnitude can be affected by coding, duplicate handling, indication, co-medication, comparator construction, masking, notoriety, stimulated reporting, and the accumulation of reports over time. READUS-PV therefore recommends transparent specification of the database, case definitions, exposure and event terms, analysis population, statistical method, sensitivity analyses, and interpretive limits; importantly, it cautions against causal wording unsupported by the design [7]. A large reporting odds ratio may be a reason to investigate, but it cannot be translated mechanically into a large absolute risk or a large treatment effect.

Temporal structure can add information that a static measure does not contain. In FAERS drug–drug interaction work, incorporating timing of co-exposure altered prioritisation of candidate triplets, showing that when drugs and events occur can change the plausibility of a statistical association [8]. This does not establish an interaction mechanism. It shows instead that numerical prominence and temporal credibility are separable dimensions of signal assessment.

The same principle applies to routinely collected healthcare data. A signal study is only as interpretable as the drug–outcome pair and design allow. A taxonomy-based implementation for real-world signal detection excluded most initially considered outcomes because detectability, outcome definition, confounding, or other design properties made them unsuitable for the intended analysis [9]. Algorithmic performance also contains trade-offs. Association-rule mining in administrative claims achieved high sensitivity under one operating rule but low specificity, demonstrating that a method can be effective at finding candidate associations while still producing a substantial false-positive burden [10]. Detection performance is therefore not a surrogate for clinical decision utility.

Spontaneous-report signals are additionally embedded in a changing reporting ecology. COVID-19 vaccine surveillance required methods adapted to rapid uptake and unusual reporting conditions; publicity was associated with marked temporal changes in suspected adverse-reaction reporting; and expansion of mandatory non-serious reporting in EudraVigilance altered database composition while producing only a modest change in detection sensitivity [11–13]. These findings do not make spontaneous-report signals intrinsically unreliable. They show why apparent signal strength must be interpreted relative to the process that generated the reports.

Scale matters as well. Resampling analyses of Vigibase demonstrated greater instability and more false-positive associations in small databases or subsets, prompting caution when disproportionality is applied to sparse strata [14]. This is especially relevant when subgroup analyses are clinically attractive but statistically thin. The implication is not that small-population signals should be ignored, but that signal strength should reflect uncertainty about the estimate rather than merely whether a threshold has been crossed.

Evidential strength

A signal becomes stronger evidentially when independent features of the suspected association cohere: case quality, temporality, dechallenge or rechallenge where informative, biological or pharmacological plausibility, consistency across sources, appropriate comparators, and robustness to alternative analytical choices. No single

feature is universally necessary or sufficient. Evidence accumulation should therefore be understood as structured convergence, not the arithmetic addition of reports.

Machine learning can assist this process, but its target must be kept visible. A supervised model developed for signal-validation classification achieved useful agreement with expert validation categories, including a prospective component, supporting a role for decision assistance [15]. The model reproduced classification patterns; it did not demonstrate that its positive classifications were biologically causal. Similarly, a Bayesian network trained for individual-case causality assessment showed strong discrimination against prior clinical judgments, but the study did not provide external validation and the prediction target was a human assessment category rather than mechanistic truth [16]. Measurement performance and causal validity are therefore distinct. The distinction between detection and prioritisation is also empirically observable. In a pilot healthcare-database system, hundreds of detected associations were progressively reduced to a much smaller set of prioritised candidates after additional criteria were applied [17]. That attrition is not a defect. It is what should happen when a sensitive detection layer is followed by an evidential and decision layer. The converse mistake is to assume that a candidate that survives detection has already survived validation.

More data do not automatically solve the problem. Simulations examining the pooling of solicited and spontaneous reports showed that combining heterogeneous sources could create or mask statistical signals depending on source composition [18]. This is a warning against naive aggregation, not against triangulation. Evidence is strengthened when sources contribute different, interpretable information and their biases are considered explicitly. It may be weakened when incompatible data-generating processes are simply pooled.

Drug–drug interaction surveillance illustrates the value of successive evidential narrowing. A VigiBase feasibility study began with hundreds of potential interaction pairs, advanced a small subset to detailed assessment, and communicated only a few signals after case-level and temporal review [19]. Non-progression should not be equated with proof that the association was false; it may reflect insufficient information, alternative explanations, or failure to meet the threshold for further action. Likewise, alternative data sources can be informative without being generally strong detectors. In WEB-RADR, broad statistical signal detection using social-media data performed near chance and below VigiBase for the tested reference sets [20]. That finding limits one use case; it does not establish that social media have no value for patient experience, hypothesis generation, or contextual understanding.

Seriousness and preventability

Evidential strength addresses how much confidence to place in an association. Seriousness addresses what may be lost if the association is real. These questions should not be merged. Designated medical events are prioritised because their clinical consequences can be severe enough to justify attention even when conventional statistical criteria are not compelling. Comparative work on designated and non-designated events supports the importance of seriousness in prioritisation while also showing that documentation quality and evidential maturity still matter [21]. Seriousness changes the cost of being wrong; it does not itself raise the probability that the medicine caused the event.

Preventability adds another layer. A hazard may be clinically important yet difficult to mitigate without sacrificing therapeutic benefit, whereas another may be addressed through monitoring, dose modification, contraindication, product selection, or targeted communication. Reviews of additional risk-minimisation measures submitted to the European Medicines Agency show that many evaluations did not permit firm conclusions about effectiveness [22]. The existence of a risk-minimisation measure therefore cannot be treated as evidence that the harm is preventable in practice.

Implementation evidence is part of that judgment. RIMES-SE explicitly distinguishes the risk-minimisation intervention from the strategy used to implement it, because fidelity, reach, adoption, and context affect interpretability [23]. Earlier systematic assessment likewise found deficiencies in the reporting of risk-minimisation programme evaluations, limiting inference about whether apparent changes represented effective mitigation [24]. Actionability should consequently reflect feasible and evidenced risk reduction where available, while preserving uncertainty when intervention effectiveness has not been demonstrated.

Magnitude and reversibility of harm

Magnitude of harm is not captured by signal prominence. It concerns the clinical consequence if the association is real, including absolute excess risk where estimable, severity, duration, functional loss, and concentration of

risk in identifiable groups. Background risk is essential because the same relative increase can have very different clinical implications across populations and time windows.

Myocarditis and pericarditis after mRNA COVID-19 vaccination illustrate why context cannot be discarded. Claims-based estimates varied by age, sex, vaccine product, dose, and the defined post-vaccination risk window [25]. These estimates are specific to the populations, outcome definitions, databases, and vaccines studied; they should not be generalized into a universal vaccine-risk magnitude. Comparative work on thrombosis with thrombocytopenia syndrome and other thromboembolic outcomes similarly found product- and database-dependent patterns, with some findings not replicated uniformly across data sources [26]. Rare-event imprecision, residual confounding, and differing background rates remain relevant. Taken together, these studies show that clinically consequential rare harms can be strongly dependent on product, population, database, and risk-window context [25, 26].

Reversibility is analytically distinct from seriousness. A serious event may be transient and treatable, whereas a less immediately dramatic event may cause persistent disability or require permanent treatment discontinuation. Pharmacovigilance datasets often characterize these dimensions incompletely, so reversibility should not be inferred from event labels alone. For this Current Opinion, the proposed decision principle is that magnitude, persistence or reversibility, and available mitigation should influence actionability independently of statistical signal strength. That is a conceptual synthesis, not a validated weighting scheme.

The practical distinction is easier to inspect as a decision-state ledger than as sequential prose, because the same statistical signal can imply different actions when background risk, bias, and reversibility differ.

Table 1. Decision-state ledger for interpreting harm magnitude and reversibility without converting signal prominence into actionability

Manuscript-derived decision state	Harm pattern requiring interpretation	Background-risk dependence	Bias or uncertainty that can distort apparent urgency	Permissible action under current uncertainty	Observation requiring reassessment	Signal-strength–actionability test
Context-sensitive rare serious harm	Clinically severe event with low absolute frequency and concentrated risk in identifiable exposure or patient strata	High; baseline incidence and subgroup composition materially affect interpretation	Outcome misclassification, sparse events, comparator imbalance, stimulated ascertainment	Targeted investigation, subgroup-specific communication, or proportionate precaution while absolute risk is clarified	Replication across well-defined populations, improved case verification, or a materially different absolute-risk estimate	Proposed — high consequence can raise actionability without converting a modest association into strong causal evidence
Large apparent association with uncertain denominator	Numerically prominent signal from a reporting system in which exposure prevalence is unavailable or poorly represented	Not directly estimable from the reporting statistic	Stimulated reporting, notoriety, duplicate or selective reporting, changing report composition	Validate phenotype, temporality, denominator-independent biases, and complementary data before major irreversible action	Stable association after bias-focused sensitivity analysis or corroboration in data with measurable exposure	Proposed — statistical prominence remains on the signal-strength axis until clinical risk magnitude is independently characterized
Product- or subgroup-dependent harm	Event burden differs across products, age groups, sex, co-exposures, or	Central; pooled averages may conceal materially	Sparse strata, residual confounding, multiplicity,	Stratified assessment and, where justified, targeted rather than	Reproducible heterogeneity with clinically interpretable exposure and	Proposed — actionability may be high for a subgroup

	other clinically defined strata	different baseline and excess risks	differential reporting	population-wide mitigation	outcome definitions	while remaining lower for the overall exposed population
Severe but potentially reversible harm	Event is serious enough to demand attention but may resolve with withdrawal, treatment, monitoring, or avoidable exposure conditions	Variable; depends on untreated event risk and feasibility of early recognition	Incomplete follow-up, uncertain dechallenge information, confounding by treatment changes	Evaluate whether monitoring or exposure modification can reduce consequence while preserving benefit	Evidence that mitigation reliably changes clinical course, or evidence of persistent harm despite mitigation	Proposed — reversibility modifies the consequence of delay but does not alter the evidential credibility of the association
Persistent or poorly reversible harm under unresolved causality	Potential long-term disability or irreversible outcome with incomplete causal evidence	Important but may be difficult to estimate for very rare phenotypes	Long latency, competing causes, incomplete longitudinal follow-up	Escalated evaluation and proportionate interim measures may be reasonable when consequences of delay are substantial	Stronger temporal, mechanistic, or epidemiological evidence; or credible evidence refuting excess risk	Proposed — severity and irreversibility can increase actionability while causal confidence remains explicitly uncertain

Patient and exposure context

The same signal may have different clinical meaning across patients because exposure is not neutral. Age, sex, renal or hepatic function, co-medication, dose, indication, treatment duration, disease severity, and availability of alternatives change both baseline risk and the consequences of intervention. Signal assessment that collapses these dimensions can dilute a vulnerable subgroup or exaggerate concern in a population with little relevant exposure. Subgroup disproportionality analyses in Vigibase have shown that reporting patterns can emerge within patient strata even when they are less apparent in aggregate data [27]. Such patterns are useful for hypothesis refinement, not individual risk prediction. A subgroup signal may reflect genuine effect modification, differential prescribing, comorbidity, reporting behavior, or residual confounding. The appropriate response is therefore to define the subgroup and competing explanations more precisely rather than to convert the stratified statistic directly into susceptibility.

Patient reports add a different form of context. Collaborative signal-detection work involving patient-reported concerns identified clinically salient information that may not be represented by statistical prominence alone [28]. Patient narratives can clarify symptom burden, functional effects, chronology, treatment disruption, and aspects of reversibility, but they cannot by themselves supply incidence denominators. Their value is complementary: they can change what decision-makers consider important even when they do not strengthen the numerical signal. Exposure context also determines what evidence is worth obtaining next. Routinely collected health data may be most informative when the unresolved question concerns incidence, comparator risk, treatment switching, or a defined risk window [3]. Product-, dose-, and subgroup-specific estimates may be decisive when harm is heterogeneous [25]. Stratified signal analyses may identify where aggregate surveillance is obscuring a pattern [27]. The proposed actionability concept therefore treats patient and exposure context as modifiers of the consequences of uncertainty, not as hidden components of a single statistical signal score.

When a strong signal is not yet actionable

A strong signal can remain weakly actionable when the evidence is impressive in volume or statistical prominence but still fails to answer the decision-relevant question. The clearest example is not necessarily a large

disproportionality statistic. It may be a substantial body of postmarketing evidence whose regulatory meaning remains context dependent. A review of large postmarketing cardiometabolic trials found that most led to safety-section updates in European product information, but a substantial minority did not [29]. The absence of an update does not mean the trials contained no safety information; it demonstrates that evidence volume alone does not determine regulatory consequence.

Several failure modes can produce this state. A strong disproportionality signal may rest on incomplete phenotype definition, stimulated reporting, or a changing reporting denominator. A signal may be internally consistent but temporally implausible. Apparent replication may arise from data sources sharing the same biases. Case-level assessment may remain limited by missing exposure dates, co-medication, competing diagnoses, or treatment switching. Conversely, a well-replicated association may be clinically difficult to act on because the absolute risk is very small, the exposed population has no reasonable alternative therapy, the suspected harm is readily reversible, or an intervention would create a larger competing risk.

The article therefore proposes a strong-signal, low-actionability state. It is not a recommendation for passivity. It is a diagnostic state indicating that the main uncertainty blocking action must be identified explicitly. Meta-research on disproportionality studies shows why validity safeguards and contextualisation matter [2]. Temporal analyses demonstrate that timing can materially change prioritisation [8]. Simulations show that heterogeneous data pooling can create misleading reinforcement [18]. Detailed Vigibase assessment of potential drug–drug interactions shows that many initial candidates do not progress after richer case and temporal review [19]. The correct next step is consequently not always to accumulate more reports; it may be to obtain the particular evidence that can resolve the blocking uncertainty.

This distinction also protects against an opposite error: treating “not yet actionable” as “not important.” A signal can deserve intensive investigation while remaining insufficient for irreversible intervention. Action itself is not binary. Enhanced surveillance, targeted data collection, expert case review, protocolized outcome validation, temporary communication, or focused subgroup analysis can be proportionate responses while the evidential question is being clarified.

The causal-bias diagnostic map below is therefore needed to show where an apparently strong signal can lose decision readiness, and where targeted evidence can restore it without equating stronger statistics with stronger clinical action.

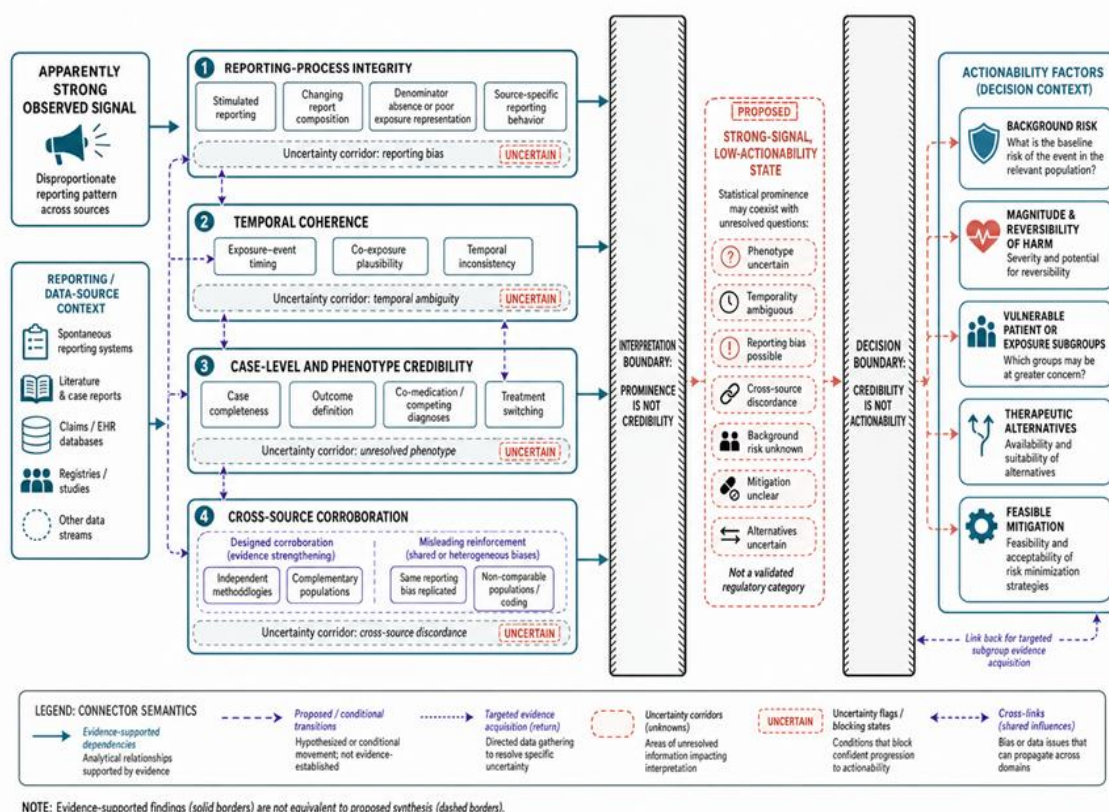


Figure 1. Where an apparently strong pharmacovigilance signal loses decision readiness

When a modest signal demands action

The converse state is equally important. A signal can be statistically modest yet clinically urgent when the possible outcome is severe, difficult to reverse, concentrated in a vulnerable group, or preventable through a low-burden intervention. Designated medical events illustrate this asymmetry: seriousness can justify early prioritisation even when conventional statistical criteria are not striking [21]. Rare myocarditis and thrombotic outcomes also show why low frequency cannot be treated as low consequence, although their interpretation remains product-, population-, and risk-window-specific [25]. Comparative vaccine data further demonstrate that clinically important patterns may differ across products and databases rather than forming a uniform class effect [26].

Regulatory communication decisions already appear to incorporate more than frequency. In a conjoint survey of European regulators evaluating SGLT2-inhibitor safety scenarios, willingness to communicate varied with several attributes of the suspected adverse reaction, including characteristics related to seriousness, causality, frequency, and evidence source [30]. The study measured stated preferences in hypothetical scenarios, not actual regulatory thresholds, but it supports the broader point that communication is multidimensional.

This Current Opinion therefore proposes a modest-signal, high-actionability state. It applies when the consequence of delayed recognition may be substantial and a proportionate, preferably reversible response is feasible. The response need not be product withdrawal. Focused communication, intensified surveillance, contraindication review, targeted monitoring, or additional evidence generation may be more appropriate. Preventability should not be presumed simply because a mitigation measure can be imagined: evaluations of risk-minimisation measures frequently leave effectiveness uncertain [22]. Actionability should therefore express the case for proportionate action under uncertainty, not certainty that the suspected association is causal.

A signal-strength–actionability matrix

Published pharmacovigilance communications arise from heterogeneous evidential pathways rather than one uniform sequence from statistical signal to regulatory consequence [31]. The article therefore proposes a two-dimensional matrix in which signal strength and clinical actionability are assessed separately. This is a reasoning framework, not a validated score, decision threshold, or regulator-endorsed classification.

On the signal-strength dimension, assessment should ask whether the association is credible given data provenance, phenotype quality, temporality, confounding, reporting processes, reproducibility, and complementary evidence. On the actionability dimension, assessment should ask what is at stake if the association is real: seriousness, magnitude and reversibility of harm, vulnerable exposure groups, available alternatives, preventability, urgency, and feasibility of proportionate intervention. These dimensions may move independently as evidence develops.

Four broad states follow conceptually. High signal strength with high actionability provides the clearest case for decisive response, subject to benefit–risk context. High signal strength with low actionability calls for identifying what prevents a useful intervention rather than mistaking evidential confidence for decision utility. Modest signal strength with high actionability supports proportionate precaution or accelerated investigation when consequences of delay are substantial. Modest signal strength with low actionability generally favors surveillance and targeted evidence acquisition. These states are proposed and dynamic: movement between them may follow better phenotype definition, subgroup identification, changing exposure, new comparative evidence, or demonstration that mitigation is or is not effective.

This separation also clarifies disagreement. Two reviewers may agree on the observed association yet disagree about action because they assign different importance to therapeutic alternatives, reversibility, subgroup vulnerability, or the consequences of delay. Conversely, they may disagree about causal credibility while still support the same temporary precaution. Making those reasons explicit is more informative than forcing both judgments into one ordinal signal category.

The matrix is deliberately non-numeric. Assigning universal weights would falsely imply commensurability among causal credibility, severity, reversibility, therapeutic necessity, and implementation feasibility. Its function is to force explicit answers to two questions that pharmacovigilance can otherwise collapse: how convincing is the signal, and what should be done given what is currently known?

Communication and regulatory use

Regulatory communication should preserve this distinction. European signal management demonstrates that detection is followed by assessment and potentially several different actions [4], while FDA label-change

experience shows that decisions can be supported by heterogeneous evidence sources [5]. Communication should therefore state separately why an association is considered credible and why a particular response is proportionate. Timing also matters. Evaluation of additional risk-minimisation measures may extend well beyond their initial implementation, so action and verification can occur on different timescales [32]. This creates a need for explicitly revisable decisions: early action may be justified under uncertainty, but its rationale, expected mitigation pathway, and evidence needed for reassessment should be visible.

Actionability also depends on whether a health system can execute the proposed response. The SCOPE Joint Action treated pharmacovigilance capability as a coordinated network function spanning reporting, signal management, risk minimisation, and communication [33]. Such infrastructure does not strengthen causal evidence directly, but it affects whether monitoring, communication, or mitigation can be implemented consistently.

Accordingly, the proposed framework should be used as a communication discipline rather than an automated rule. Statistical prominence should not be translated into causal certainty, and clinical urgency should not be misrepresented as evidential certainty. Separating the two permits regulators, clinicians, manufacturers, and patients to understand both why a signal is believed and why action is—or is not—being taken.

CONCLUSION

Pharmacovigilance decisions are weakened when statistical signal strength is allowed to stand in for clinical actionability. Evidence supporting an association and reasons for intervention overlap, but they are not the same construct. The proposed separation makes uncertainty more explicit, accommodates serious but statistically modest concerns, and explains why analytically strong signals can remain poorly suited to immediate irreversible action. Its value is conceptual rather than predictive: it supplies no universal thresholds, weights, causal algorithm, or regulatory mandate. Future evaluation should test whether separating evidential credibility from consequence-sensitive action improves consistency, transparency, and revisability of real pharmacovigilance decisions without encouraging either premature intervention or avoidable delay.

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