



How RWE can better support pharmacovigilance signal management

Niklas Norén, Chief Science Officer
Uppsala Monitoring Centre

Pharmacovigilance



Individual case reports

Report of Suspected Adverse Drug Reaction including Birth Defects **224289**

(Note: Identities of Reporter, Patient and Institution will remain Confidential)

Patient (Initials or Record, only) Age Sex Weight Height
[REDACTED] 05 DEC 2006 55 M 80 168

Adverse Reaction Description: DESC Date of Onset of Reaction: 29/11/06
Patient with a NON ST ELEVATION MI HAD DIAGNOSTIC ANGIOGRAM SHOWING SEVERE STENOSIS IN LAD. THE SAME DAY HAD PCI TO LAD DURING WHICH EXPERIENCED PROFOUND AND SUSTAINED HYOTENSION NOT BELIEVED WITH AMARINE 6mg (several 0.5mg boluses) AND IABP. IMPROVED AFTER HYDROCHLORIDE 200mg + PHENERGAN GIVEN. ??ALLERGIC REACTION TO CONTRAST GIVEN. (ISSUE 370)

All Drug Therapy Prior to Reaction Asterisk Suspected Drug(s) (please use trade names)	Daily Dosage and Route	Date Begun	Date Stopped	Reason for Use
<u>ASPIRIN</u>	300mg o	29/11/06	—	NSTEMI
<u>CLOPIROGREL</u>	300mg o	29/11/06	—	NSTEMI
<u>TEMAZEPAM</u>	10mg	29/11/06	—	Sedation
<u>Tirofiban</u>	IV bolus + infusion	29/11/06	29/11/06	NSTEMI
<u>MLAZOLAM</u>	2mg IV	29/11/06	29/11/06	Sedation
<u>OMNIVIQUE</u>	90mg IC	29/11/06	29/11/06	ANGIOGRAM
<u>ISSUE 370</u>		29/11/06	29/11/06	ANGIOGRAM

Treatment (of reaction): AMARINE, HYDROCHLORIDE, PHENERGAN

Outcome: Recovered ☒ Not Yet Recovered ☐ Unknown ☐ Fatal ☐ Date of Death 1/1

Sequelae: No ☒ Yes ☐ (describe) MYOCARDIAL INFARCTION

Comments (eg. relevant history, allergies, previous exposure to this drug):
NO KNOWN ALLERGIES BEFORE THE EPISODE. HAD ANGIOGRAM IN ANOTHER HOSPITAL. THEN PCI SAME DAY. REACTION DURING PCI.

Reporting Doctor, Pharmacist, etc:
Name: [REDACTED]
Address: [REDACTED]

Signature [REDACTED] 30/11/06



Routinely collected health data

- Denominators
 - Number of patients exposed to medicine
 - Rates of adverse event with and without exposure to medicines
- Ability to assess more complex associations
 - Adjustment for biases and confounding
 - Incl due to indication or underlying disease
- Longitudinal data capture (before and after adverse event)



Features of case reports that support putative causal relationships between medicinal products and suspected adverse drug reactions. Preliminary results from a scoping review

Daniele Sartori¹, Jeffrey K. Aronson², Igho J. Onakpoya³

Background

Bradford Hill's viewpoints, as he called them, also called guidelines, can be used to help determine whether an adverse event can form the basis of a pharmacovigilance signal. Beside a few applications of the viewpoints, little has been done to study which features of reports most often support such assessments.

Objectives

To characterise the features of reports of adverse events used to support signals of suspected adverse drug reactions (ADRs).

When reports were screened these 3 features stood out as signs of a signal



Positive dechallenge/rechallenge
Withdrawal of treatment results in improvement or complete resolution of the event; re-introduction results in recurrence.



Temporality
Occurrence of an event within a plausible, clinically compatible, time window following drug administration.



Exclusion of competing causes
(a) No other medicines are reported as possible suspects;
(b) Availability of a sufficiently detailed medical history/free text information to rule out other conditions as triggers of the event.

Signals

Methods

We retrieved electronic records (PubMed, EMBASE, Web of Science, PsycINFO) and grey literature records that described findings as signals of ADRs or signals of disproportionate reporting, without time or language restrictions; when necessary, we contacted regulatory agencies and authors to obtain other records or clarifications. We included previously undocumented signals and excluded records that did not explicitly describe findings as signals. We also charted the features of reports of suspected ADRs that authors advanced as supportive of signals and when possible coded them to mirror the Bradford Hill viewpoints, omitting biological plausibility and strength of association. One author performed title/abstract screening, eligibility assessment, and data charting; a second author independently cross-validated the findings. We analysed the data descriptively.

Results

We screened the titles/abstracts of 9525 electronic records and the full texts of 1509. We also reviewed the full texts of 2249 entries from websites/cited references/original authors, and included 1721 in the review. In all, we screened 11,774 unique records and included 2125. Of those, 1081 concerned clinical reviews of reports of ADRs (either alone or with other types of evidence); 136 of these mentioned at least one feature and concerned 228 distinct signals: 88 presented one feature, 80 two, 48 three, and 12 > three. We recorded 440 instances of relevant features; the most frequent was positive dechallenge/positive rechallenge (217 occurrences), followed by temporality (130) and exclusion of competing causes/only one suspect drug in a report (53). Other signals depended on available information to ascertain the suspected ADRs (15), the report's consistency (12), and biological gradient (6).

Conclusions

In this scoping review positive dechallenge/rechallenge, temporality, and exclusion of competing causes were the most frequent factors supporting signals



2025: Case reports continue to dominate as a source of safety signals

How come?

Drug Safety
<https://doi.org/10.1007/s40264-022-01258-0>

SCOPING REVIEW

Signals of Adverse Drug Reactions Communicated by Pharmacovigilance Stakeholders: A Scoping Review of the Global Literature

Daniele Sartori^{1,2} · Jeffrey K. Aronson² · G. Niklas Norén¹ · Igho J. Onakpoya³

Accepted: 10 November 2022

Sartori et al.
2023

Onakpoya et al. 2016

Onakpoya et al. BMC Medicine (2016) 14:10
DOI 10.1186/s12916-016-0553-2



Medicine and the Future of Health

RESEARCH ARTICLE

Open Access



Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature

Igho J. Onakpoya^{*}, Carl J. Heneghan and Jeffrey K. Aronson

Abstract

Background: There have been no studies of the patterns of post-marketing withdrawals of medicinal products to which adverse reactions have been attributed. We identified medicinal products that were withdrawn because of adverse drug reactions, examined the evidence to support such withdrawals, and explored the pattern of withdrawals across countries.

Methods: We searched PubMed, Google Scholar, the WHO's database of drugs, the websites of drug regulatory authorities, and textbooks. We included medicinal products withdrawn between 1950 and 2014 and assessed the levels of evidence used in making withdrawal decisions using the criteria of the Oxford Centre for Evidence Based Medicine.

Results: We identified 462 medicinal products that were withdrawn from the market between 1953 and 2013, the most common reason being hepatotoxicity. The supporting evidence in 72 % of cases consisted of anecdotal reports. Only 43 (9.34 %) drugs were withdrawn worldwide and 179 (39 %) were withdrawn in one country only. Withdrawal was significantly less likely in Africa than in other continents (Europe, the Americas, Asia, and Australasia and Oceania). The median interval between the first reported adverse reaction and the year of first withdrawal was 6 years (IQR, 1–15) and the interval did not consistently shorten over time.

Conclusion: There are discrepancies in the patterns of withdrawal of medicinal products from the market when adverse reactions are suspected, and withdrawals are inconsistent across countries. Greater co-ordination among drug regulatory authorities and increased transparency in reporting suspected adverse drug reactions would help improve current decision-making processes.

Keywords: Adverse drug reaction, Drug withdrawal, Systematic review, Voluntary recall

Background

Drug regulatory authorities award marketing authorization that license pharmaceutical companies to market medicinal products when there is sufficient evidence that the product has a favourable benefit-to-harm balance [1]. If a new adverse drug reaction is suspected after approval, several courses of action can be taken by the regulator and/or manufacturer, including adding a new product

label with specific warnings [2], adding a new contraindication [3], issuing a Direct Healthcare Professional Communication [4], allowing patients to decide whether they will take the drug [5], and in the most serious cases, withdrawal or revocation of the licence [6].

Post-approval withdrawal of medicinal products because of adverse drug reactions can be triggered by evidence obtained from various sources – anecdotal reports, observational studies, clinical trials, systematic reviews, or animal data. The removal of previously approved products from the market can result in loss of confidence in medicines by the public, loss of effective

* Correspondence: igho.onakpoya@phc.ox.ac.uk
Centre for Evidence-based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, New Radcliffe House, Radcliffe Observatory Quarter, Oxford OX2 6GG, UK



© 2016 Onakpoya et al. **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

REVIEW OPEN ACCESS

Recommendations to Enable Broader Use of Real-World Evidence to Inform Decision-Making Throughout Pharmacovigilance Signal Management

G. Niklas Norén¹ | Katherine Donegan² | Monica A. Muñoz³ | Thamir M. Alshammari⁴ | Nicole Pratt⁵ | Gianmario Candore⁶ | Daniel Morales⁷ | Peter Rijnbeek⁸ | Andrew Bate⁹ | Rodrigo Postigo⁷ | Sengwee Toh^{10,11} | Gianluca Trifiro¹² | Montse Soriano Gabarro⁶ | Alison Cave² | Patrick B. Ryan¹³

¹Uppsala Monitoring Centre, Uppsala, Sweden | ²Medicines and Healthcare Products Regulatory Agency, London, UK | ³US Food and Drug Administration, Silver Spring, Maryland, USA | ⁴Jazan University, Jazan, Saudi Arabia | ⁵University of South Australia, Adelaide, Australia | ⁶Bayer AG, Berlin, Germany | ⁷European Medicines Agency, Amsterdam, the Netherlands | ⁸Erasmus University Medical Center, Rotterdam, the Netherlands | ⁹GSK, London, UK | ¹⁰Harvard Medical School, Boston, Massachusetts, USA | ¹¹Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA | ¹²University of Verona, Italy | ¹³Janssen Research and Development, Titusville, New Jersey, USA

Correspondence: G. Niklas Norén (niklas.noren@who-umc.org)

Received: 2 December 2024 | **Revised:** 29 May 2025 | **Accepted:** 23 September 2025

Funding: This work was supported by the International Society of Pharmacoepidemiology.

Keywords: decision-making | pharmacovigilance | real-world data | real-world evidence | regulatory science | signal management

ABSTRACT

Introduction: Despite substantial investments in analytical infrastructure and scientific research related to the development and analysis of real-world evidence in support of signal management, the impact on routine pharmacovigilance activities has been limited. Most organizations still rely largely on analyses of individual case reports and pre-existing evidence – especially during signal detection and validation.

Objective: This paper presents a set of recommendations for efforts to enable broader use of real-world evidence throughout pharmacovigilance signal management, in the future.

Outcome: The recommendations regard streamlined data access, data harmonization and use of reproducible analytical workflows to enable rapid and robust evidence generation. They emphasize the need for cross-disciplinary collaboration and for organizational adaptations to ensure adequate competence and supporting processes, including principles for how to integrate new types of evidence in decision-making. The execution of pilot studies under realistic conditions and the dissemination of their findings are highlighted as important steps toward defining the proposed change and driving progress in this area. This manuscript is endorsed by the International Society for Pharmacoepidemiology (ISPE).

1 | Background

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other problem related to medicinal products. Medicinal products approved for regular clinical use must

be continually monitored for new information that may alter their benefit-risk balance overall and/or in different settings and populations. To this end, regulatory authorities, pharmaceutical companies, and other stakeholders analyze an array of data sources to detect information that may suggest previously unknown risks of adverse effects or new information about

Summary

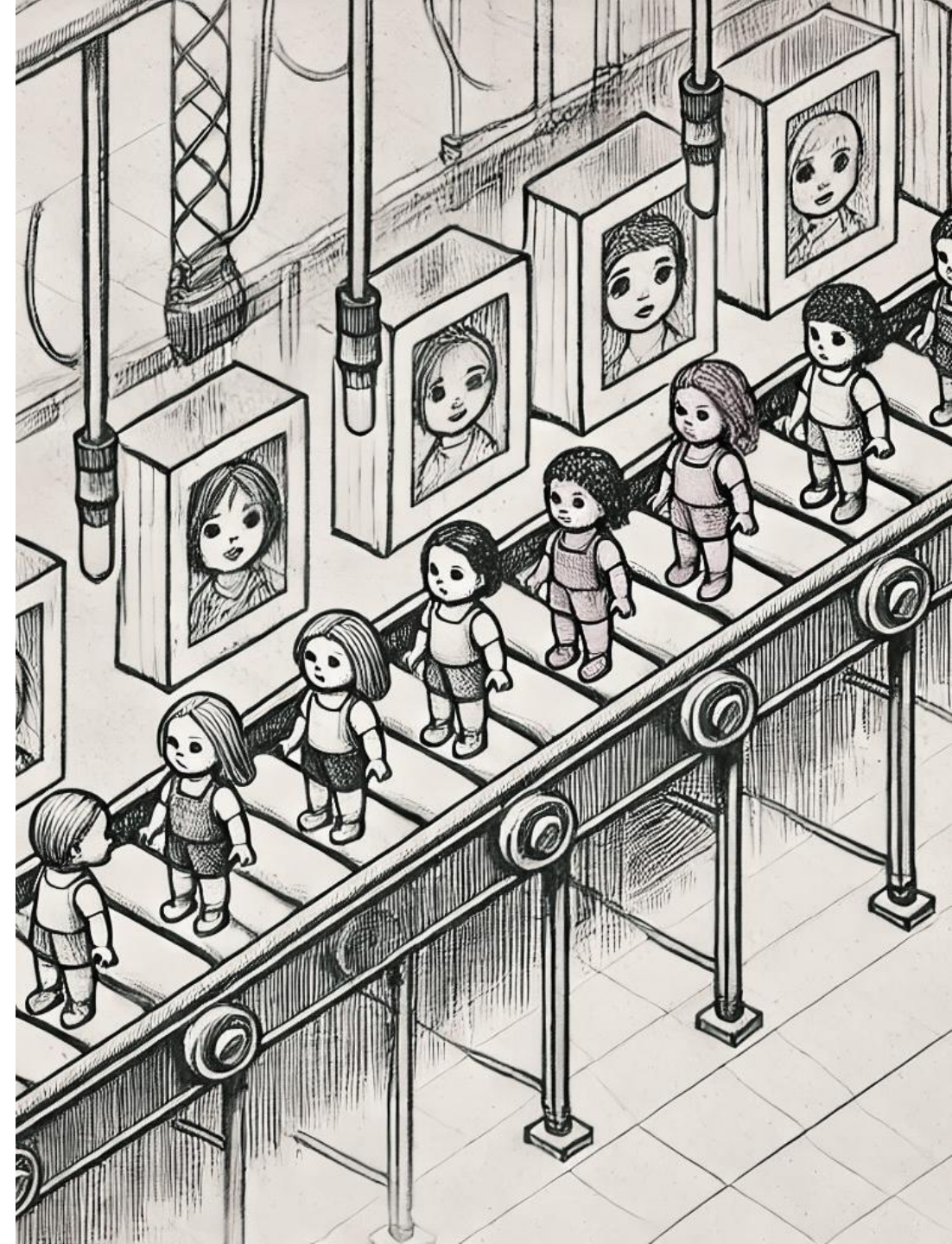
- Substantial investments have been made to support the development and analysis of real-world evidence for regulatory decision-making
- Even so, most pharmacovigilance organizations rely primarily on individual case reports and preexisting evidence during signal management
- Streamlined access to fit-for-purpose data, data harmonization, and the use of reproducible analytical workflows are identified as enablers of rapid and robust evidence generation using real-world data
- Impact on pharmacovigilance decision-making may depend on cross-disciplinary collaboration and the establishment of principles for evidence integration
- The execution of pilot studies and dissemination of their findings can help drive progress

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2025 The Author(s). *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons Ltd.

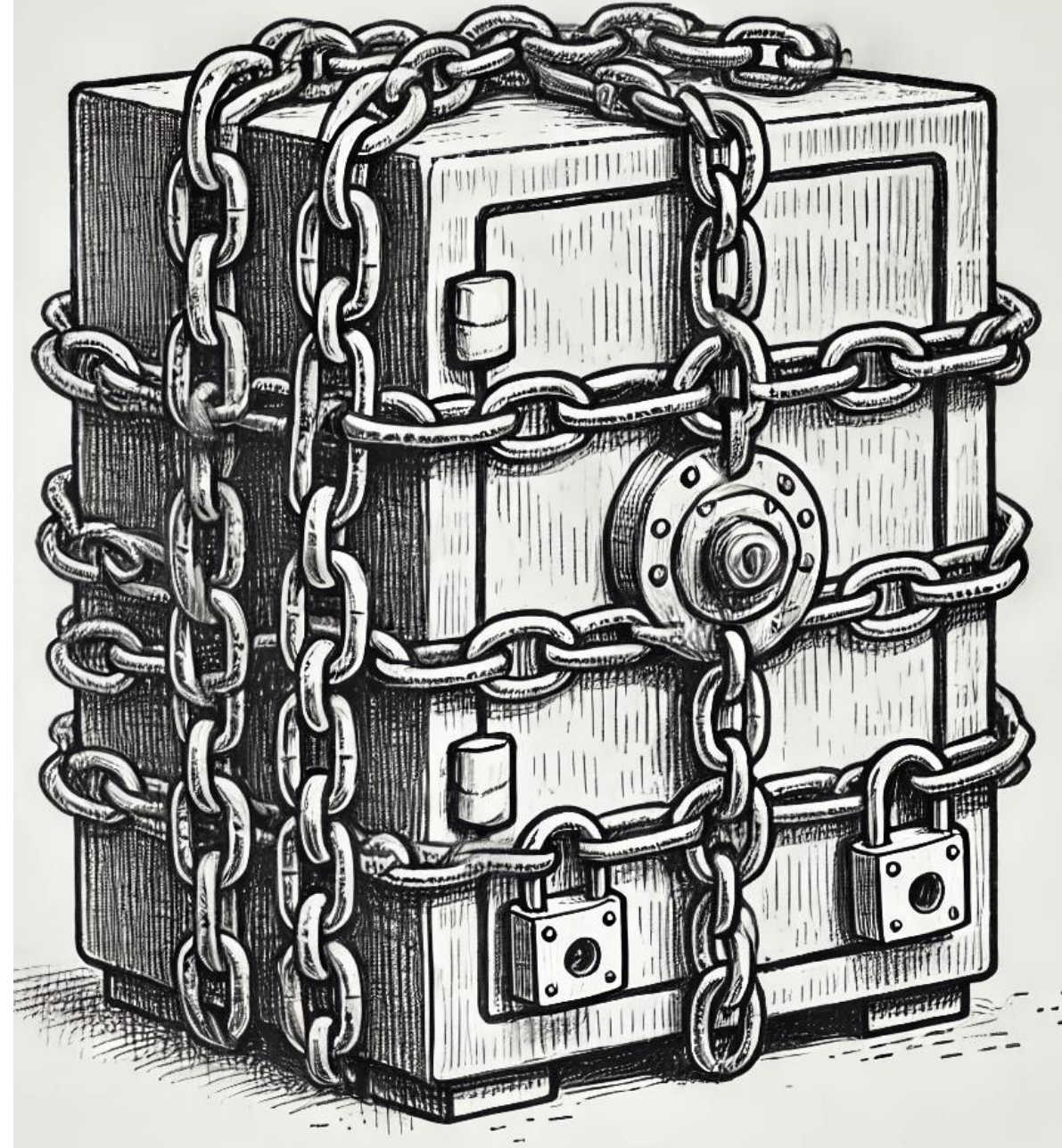
Needed: Rapid and reliable evidence-generation

- Datasets mapped to broadly used Common Data Models, including their standard vocabularies
- Reproducible analytical workflows with possibility to customise design parameters for pharmacovigilance use case
- Validated phenotypes for broad range of outcomes and covariates
- + capability to develop and deploy new phenotypes in response to findings



Needed: Timely access to fit-for-purpose data

- Data on relevant medicinal products and adverse events for the right patient populations
- Streamlined data access approval processes
- Harmonized requirements for study protocols across RWD sources
- Data access approval for overarching study designs/master protocols for pharmacovigilance use cases



Needed: Process adaptations

- Collaboration between pharmacovigilance, epidemiology, and RWD expertise
- Guidance on how to integrate new types of evidence in current processes







*Safer use of medicines
and vaccines for
everyone everywhere*



*Safer use of medicines
and vaccines for
everyone everywhere*



*Safer use of medicines
and vaccines for
everyone everywhere*



*Safer use of medicines
and vaccines for
everyone everywhere*



*Safer use of medicines
and vaccines for
everyone everywhere*