A Textbook of Pharmacoepidemiology and Pharmacovigilance for Pharmacy Students

Lesson 10: Pharmacovigilance

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10.1. Pharmacovigilance

Pharmacovigilance is the scientific discipline and set of activities dedicated to identifying, evaluating, understanding, and preventing adverse effects resulting to the use of drugs. It plays a role in ensuring that the **benefits** of medicines outweigh their **risks**, contributing to safer and more rational use of therapeutic agents in society. The term itself originates from the Greek word *pharmakon*, meaning medicine or drug, and the Latin word *vigilia*, meaning to keep watch or stay vigilant, together capturing the essence of “keeping watch over medicines”.

The conceptual foundation of pharmacovigilance can be traced to the nineteenth century, when medical practice began to record and analyze adverse consequences of treatment. The first documented event regarded as a issue in drug safety occurred in 1848 when a fifteen-year-old girl (named Hannah Greener) died after receiving chloroform anesthesia during a minor surgical procedure. Following similar incidents, The Lancet established a commission that collected reports of anesthesia-related deaths, marking the earliest organized attempt to monitor adverse drug reactions[1].

Pharmacovigilance as a formal discipline, however, only emerged in the twentieth century. The sulfanilamide tragedy of 1937 in the United States, in which more than one hundred people died from diethylene glycol, a toxic solvent used in a new formulation, prompted the enactment of the 1938 Food, Drug and Cosmetic Act, giving the U.S. Food and Drug Administration authority to ensure drug safety (See Lesson 1: Foundations of Pharmacoepidemiology). A few decades later,

[1] Report of the Lancet commission appointed to investigate the subject of the administration of chloroform and other anesthetics from a clinical standpoint. Lancet. 1893;141(3629):629-638. doi: 10.1016/S0140-6736(02)02258-4

the thalidomide disaster of the early 1960s, characterized by thousands of congenital malformations in babies born to mothers who had taken thalidomide during pregnancy, served as the catalytic turning point for the establishment of modern pharmacovigilance systems. In its aftermath, regulatory vigilance became a cornerstone of pharmaceutical governance, leading to sweeping reforms such as the 1962 U.S. Kefauver–Harris Amendments requiring proof of both efficacy and safety before marketing.

The global consolidation of pharmacovigilance followed. In 1964, the United Kingdom introduced the **Yellow Card Scheme**, allowing physicians to report suspected adverse drug reactions voluntarily. Four years later, the **World Health Organization** launched the **Programme for International Drug Monitoring,** establishing the Uppsala Monitoring Centre in Sweden as a hub for international data exchange and signal detection[2]. These developments established the integrated framework that sustains pharmacovigilance today.

Pharmacovigilance thus evolved from a reactive effort to a proactive scientific system embedded throughout the drug life cycle, from clinical development and approval to post-marketing surveillance. Pharmacovigilance extends beyond recording adverse reactions to include **continuous assessment of the risk–benefit balance**, timely **communication of safety information**, and the **implementation of risk minimization strategies**.

10.2. Core Concepts and Terminology

10.2.1. Adverse drug events vs. Adverse drug reactions

In pharmacovigilance, the difference between **adverse events** and **adverse drug reactions (ADRs)** is highly relevant. Although the two terms are often used interchangeably in casual speech, they have distinct scientific and regulatory meanings that are crucial to accurate drug safety assessment.

An **adverse event** refers to any problematic medical occurrence that happens during treatment with a medicinal product, regardless of whether it has a causal relationship with that treatment. In other words, an adverse event is something undesirable that occurs after taking a drug but is not necessarily caused by it. Examples include events such as a car accident, headache, or viral infection that happen during a clinical trial while the participant is on active therapy. These occurrences are temporally associated with the treatment but may be unrelated to the drug's pharmacological action. The International Conference on Harmonization (ICH E2D) and the WHO both define an adverse event as "**any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product**".

By contrast, an adverse drug reaction (ADR) is defined as a harmful and unintended response to a medicinal product that is causally related to its use. According to the WHO definition[3], an ADR is "**a response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function**". The key determinant is the causal relationship

[2] https://who-umc.org/about-the-who-programme-for-international-drug-monitoring/
[3] WHO. International Drug Monitoring: the role of national centers (1972). https://who-umc.org/media/2680/who-technical-report-498.pdf

between the drug and the event. If causality is established or reasonably suspected, the event is classified as an ADR. For example, a patient who develops a rash due to penicillin allergy experiences an ADR, whereas another patient who catches influenza while on penicillin experiences an adverse event.

Pharmacovigilance systems must capture both AEs and ADRs, but their reporting requirements may differ. Adverse events are reported systematically in clinical trials, where every medical occurrence after product administration is documented, while ADRs become the focus in post-marketing surveillance, when the causal relationship is more central to public health analysis. Accurate differentiation between these entities enables clear signal detection, appropriate causality assessment, and rational regulatory decision-making.

10.2.2. Medication errors and Adverse drug events

Understanding the differences between medication errors and adverse drug events (ADEs) is critical for designing preventive safety systems and ensuring accurate reporting in pharmacovigilance practice.

A **medication error** is defined as **any preventable event that may cause or lead to inappropriate medication use or patient harm while the drug is under the control of a healthcare professional, patient, or consumer**. Errors can occur at any stage of the medication-use process (i.e., prescribing, transcribing, dispensing, preparation, administration, or monitoring), and may involve omissions, miscommunication, or incorrect execution of an intended action. These errors may be due to human factors such as misinterpretation, workflow pressures, or system design flaws. Importantly, **medication errors are not synonymous with harm**: many are intercepted before reaching the patient (so-called **near misses**), while others result in no clinical injury despite occurring.

An **adverse drug event** is a broader concept that encompasses any injury resulting from any intervention related to a drug. This includes both harm directly caused by a drug's pharmacologic activity (adverse drug reactions) and harm from errors in prescribing or administration, such as overdoses or incorrect routes of delivery. **All ADEs, by definition, involve patient harm, but not all are due to errors**.

In practice, adverse drug events can be subclassified into three functional categories:

- Preventable ADEs: Result from medication errors (e.g., administering the wrong dose leading to hypoglycemia).
- Non-preventable ADEs: Correspond to adverse drug reactions (e.g., allergic anaphylaxis to penicillin).
- Potential ADEs: Errors that could have caused harm but were intercepted before reaching the patient.

The interplay between these phenomena forms a hierarchy: all adverse drug reactions are adverse drug events, but not all ADEs are ADRs, and not all medication errors lead to adverse drug events.

10.2.3. Classification of Adverse Drug Reactions

The classification of **adverse drug reactions (ADRs)** provides a framework for understanding their underlying mechanisms, clinical patterns, and predictability. The most widely accepted

system, first proposed by Rawlins and Thompson[4] in the 1970s and later refined by Edwards and Aronson[5], categorizes ADRs according to their relationship to dose, timing, and patient susceptibility. This classification helps clinicians and pharmacovigilance professionals interpret causality, anticipate potential adverse effects, and distinguish between predictable pharmacologic outcomes and idiosyncratic reactions.

Type A: Augmented Reactions

Type A reactions are **dose-dependent and predictable** from the known pharmacologic action of the drug. They are the most common, accounting for approximately 80–90% of ADRs. Because they occur with high frequency and are generally preventable, they are of primary focus in dose optimization and therapeutic drug monitoring. Common subtypes include:

- **Overdosage**: Excessive dose or accumulation (e.g., acetaminophen overdose causing hepatotoxicity).
- **Side effects**: Expected but often undesirable pharmacologic effects at therapeutic doses (e.g., constipation from opioids).
- **Secondary pharmacologic effects**: Indirect effects resulting from the drug's action, but not directly (e.g., candidiasis following antibiotic-induced flora disruption).
- **Drug–drug or drug–food interactions**: Synergistic or antagonistic pharmacodynamic or pharmacokinetic interactions (e.g., increased bleeding risk with warfarin and aspirin).

Type B: Bizarre Reactions

Type B reactions are **idiosyncratic, dose-independent, and unpredictable** based on known drug actions. They occur in a small subset of susceptible individuals and account for about 10–15% of ADRs. These reactions are often immune-mediated or genetically determined. Examples include:

- **Allergic (immune) reactions**: IgE-mediated anaphylaxis with penicillin, or delayed hypersensitivity dermatitis with carbamazepine.
- **Idiosyncratic (non-immunologic) reactions**: Hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency or malignant hyperthermia triggered by halothane.

Type C: Chronic Reactions

Type C reactions are dose- and time-related, **typically arising after prolonged use or cumulative exposure**. They are often associated with chronic therapy rather than acute dosing. Examples include adrenal suppression (pseudo-Cushing) during long-term corticosteroid therapy or tardive dyskinesia from chronic antipsychotic use.

Type D: Delayed Reactions

Type D reactions **appear after a delay, which may be weeks, months, or even years following exposure**. These may result from mutagenic or carcinogenic mechanisms or long-term tissue

[4] Rawlings MD, Thompsom JW. Pathogenesis of adverse drug reactions. In: Davies DM, ed. Textbook of adverse drug reactions. Oxford: OUP; 1977.
[5] Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259. doi:10.1016/S0140-6736(00)02799-9

accumulation. Examples include secondary cancers from alkylating chemotherapeutic drugs or teratogenic effects from thalidomide exposure.

Type E: End-of-Use (Withdrawal) Reactions

Type E reactions **arise following drug withdrawal**, when physiological adaptations to chronic treatment are suddenly reversed. Examples include rebound hypertension after abrupt cessation of clonidine or adrenal crisis after rapid withdrawal from corticosteroid therapy.

Type F: Failure of Therapy

Type F reactions refer to **unexpected therapeutic failures**, often due to drug interactions, bioavailability problems, or the development of tolerance or resistance. Examples include antibiotic failure due to microbial resistance or loss of contraceptive effect when oral contraceptives are co-administered with enzyme inducers such as rifampicin.

10.2.4. Seriousness vs. Severity

Although often mistaken as interchangeable, **seriousness** and **severity** describe fundamentally different aspects of an adverse drug reaction.

Seriousness is a regulatory concept defined by the International Council for Harmonisation (ICH E2D) and adopted globally in pharmacovigilance frameworks such as those of the European Medicines Agency and the WHO. **Seriousness refers to the outcome or potential consequences an ADR has for the patient**, rather than the magnitude of symptoms. An event is **classified as serious if it meets one or more of these criteria**:

- Results in death
- Is life-threatening at the time of the event (not hypothetically)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Causes a congenital anomaly or birth defect
- Is a medically important event that, while not immediately life-threatening, could jeopardize the patient or require intervention to prevent one of the above outcomes

Thus, seriousness reflects the impact of the event on patient safety and public health, rather than how “bad” the symptoms appear. For example, a myocardial infarction is serious because it is life-threatening, while even mild cases must be urgently reported to regulators.

Severity, on the other hand, **denotes the clinical intensity or degree of a reaction and not its medical significance**. It is a clinical descriptor, indicating **how strongly a reaction manifests** or how much it interferes with daily activities. **Commonly graded as mild, moderate, or severe**, severity is independent of regulatory classification. For example:

- **Mild**: Symptoms cause minimal discomfort and do not limit normal activities (e.g., mild rash).
- **Moderate**: Symptoms interfere somewhat with daily life or may require minimal medical intervention (e.g., moderate nausea).
- **Severe**: Symptoms are incapacitating or require intensive management (e.g., severe asthma attack).

A reaction can therefore be **severe without being serious** (e.g., severe headache) or **serious without being severe** (e.g., asymptomatic, lab-detected hepatic enzyme rise requiring hospitalization).

From a pharmacovigilance point of view, **seriousness determines reporting urgency**, as serious ADRs must be rapidly communicated to national and international drug safety agencies, while **severity guides clinical management**, helping clinicians assess treatment modifications or supportive care needs.

10.3. Methods of Pharmacovigilance

Unlike pre-marketing clinical trials, which capture only a limited range of safety data from controlled populations, post-marketing surveillance aims to identify rare, delayed, or population-specific adverse effects once a drug is widely used. The methods of pharmacovigilance range from spontaneous (passive) reporting to more structured strategies such as active surveillance, targeted reporting, and record linkage. Each method contributes uniquely to the collective ability to detect safety signals, complementing one another in building a comprehensive pharmacovigilance system.

10.3.1. Spontaneous (passive) reporting

Spontaneous reporting systems represent the basis of international pharmacovigilance systems, serving as the earliest and most widespread method for detecting new or unexpected ADRs after marketing authorization. This approach relies on **voluntary communication of suspected ADRs by healthcare professionals, patients, or pharmaceutical companies** to national pharmacovigilance centers or regulatory authorities. Reports are collected into databases such as the **WHO's VigiBase**, the European **EudraVigilance**, and the FDA's **FAERS** systems, which allow for large-scale analysis of **individual case safety reports** (ICSRs).

The main strength of spontaneous reporting lies in its capacity to identify rare and serious adverse reactions that may not emerge during clinical trials. However, its passive nature introduces limitations, most notably **underreporting**, estimated in some studies to exceed 90%. Additional challenges include reporting bias, incomplete clinical data, and difficulty in establishing causality based solely on individual reports. Despite these drawbacks, spontaneous reporting remains essential for signal detection, using statistical methods such as disproportionality analysis, including Proportional Reporting Ratios (PRR) and Reporting Odds Ratios (ROR), to identify drug-event combinations that occur disproportionately often compared to background frequency.

National initiatives such as **INFARMED's Portal RAM** in Portugal, **Yellow Card Scheme** in the UK, and **MedWatch** in the United States encourage reporting by simplifying procedures and providing online submission tools. Increasingly, pharmacovigilance systems also integrate patient reporting and digital platforms, broadening the capture of real-world safety data and promoting shared responsibility in medication safety monitoring.

10.3.2. Active surveillance (registries, sentinel systems)

Active surveillance represents a proactive and systematic approach to pharmacovigilance, designed to **actively seek information on adverse drug reactions** rather than waiting for spontaneous reports. Unlike passive methods, active surveillance utilizes pre-defined protocols

to monitor specific drugs, populations, or therapeutic areas in real-world practice. This approach helps quantify the incidence of ADRs, establish causal relationships more robustly, and identify risks that may not emerge in spontaneous reporting systems.

Active surveillance is based on the continuous or periodic assessment of patient data through organized data sources such as **registries**, **sentinel sites**, or **electronic health records**. **Sentinel systems** consist of strategically chosen healthcare institutions, such as hospitals, dialysis units, or specialized treatment centers, where detailed and standardized ADR data are collected. These sites allow in-depth clinical review and the identification of safety problems in specific patient subgroups, such as those using biologics or orphan drugs. The main advantages of sentinel systems include high-quality data and rapid signal validation, though they are limited by small sample size and higher operational costs.

The Farmacias Centinela Network (Spain)

The Farmacias Centinela initiative in Spain exemplifies how community pharmacies can function as **sentinel surveillance sites** within the broader pharmacovigilance network. Established progressively across autonomous communities such as Castilla y León, Madrid, and Catalonia, these sentinel pharmacies **actively collect** safety-related information on the use of medicines, medication errors, and adverse drug reactions detected during routine dispensing activities.

Each participating pharmacy is strategically selected based on demographic and healthcare criteria to ensure representative geographic coverage, balancing urban and rural settings. Pharmacists join voluntarily after completing specialized training in pharmacovigilance and medication safety, coordinated by regional pharmacovigilance centers. Once incorporated, they monitor and report medication-related incidents, such as dispensing errors, inappropriate use, or potential therapeutic failures, using standardized reporting tools like the *Tarjeta Amarilla* system and regional digital platforms.

The Catalonia network, for instance, comprises around 75 sentinel pharmacies, covering approximately 2.5% of the population and serving as a model of representativeness and data quality in Europe. These pharmacies contribute to early detection of safety trends, including the misuse of over-the-counter drugs and the adverse effects of newly marketed therapies. During the COVID-19 vaccination campaign, the Castilla y León sentinel pharmacies collaborated in sero-prevalence and vaccine safety studies, demonstrating the flexibility and value of pharmacy-based surveillance for real-time public health monitoring.

Jambrina AM, Rams N, Rius P, et al. Creation and implementation of a new sentinel surveillance model in pharmacy offices in southern Europe. Int J Environ Res Public Health. 2022;19(14):8600. doi:10.3390/ijerph19148600

Patient registries, compile longitudinal data on individuals exposed to a specific medicinal product or those with a defined disease condition. Registries permit systematic follow-up of outcomes such as pregnancy exposures, vaccine safety, or post-marketing monitoring of novel therapies. They facilitate robust incidence estimation, enable stratified risk analysis, and provide denominator data, essential for quantifying ADR frequency and severity. Examples include the EU pregnancy registries and post-authorization safety study networks guided by EMA Good Pharmacovigilance Practices (GVP) Module VIII.

Another form, **cohort or prescription event monitoring** (PEM), tracks adverse events by linking drug dispensing data with medical encounter records or laboratory results, supporting early signal identification for newly marketed medicines. While active surveillance is resource-intensive, requiring trained personnel, data infrastructure, and standardized protocols, event monitoring remains the most precise approach for **validating signals** detected through passive systems and for ensuring safety in high-risk or underrepresented populations.

10.3.3. Record linkage and use of big data in ADR detection

Record linkage and **big data analytics** represent modern extensions of pharmacovigilance, enabling detection of adverse drug reactions through integration and real-time analysis of massive healthcare datasets. The process of **record linkage refers to systematically connecting data from different healthcare sources that pertain to the same individual**, such as hospital discharge records, electronic health records (EHRs), laboratory results, pharmacy dispensing databases, and mortality registries. By merging these sources, researchers can identify drug-event associations that would otherwise remain hidden in fragmented data systems.

The principal advantage of record linkage lies in its **ability to quantify ADR incidence in real-world populations**, including rare, delayed, or long-term outcomes not captured in controlled clinical trials. Linkage-based pharmacoepidemiologic studies typically employ cohort or case-control designs, using automated case identification algorithms and validated diagnostic codes (e.g., ICD-10, SNOMED CT) to detect possible drug-event pairs.

Big data approaches extend traditional record linkage by leveraging large-scale, heterogeneous data, ranging from EHRs and insurance claims to genomic profiles, social media posts, and wearable device metrics. When analyzed using artificial intelligence or machine learning methods, these datasets allow continuous pharmacovigilance, uncovering safety signals more rapidly and comprehensively than manual review systems. **Natural language processing (NLP) tools** enable extraction of ADR mentions from unstructured clinical narratives or online health forums, supplementing structured pharmacovigilance reports.

However, the use of record linkage and big data introduces challenges including ensuring data quality, handling privacy-sensitive information, and controlling for confounding. Algorithms must be rigorously validated to avoid false signal generation, and governance frameworks like the EU General Data Protection Regulation (GDPR) impose strict standards for ethical data use. Despite these limitations, the integration of large-scale data analytics has transformed pharmacovigilance into a predictive and dynamic discipline, bridging classical epidemiology with computational science to protect patient safety more effectively.

10.4. Pharmacovigilance Systems

Pharmacovigilance systems constitute the institutional and procedural backbone of global drug safety. They are **organized frameworks through which medicines are systematically monitored after authorization to identify, assess, and mitigate risks associated with their use[6].** Pharmacovigilance systems ensure continuous post-marketing oversight under real-world

[6] EMA pharmacovigilance system. https://www.ema.europa.eu/en/documents/other/european-medicines-agency-pharmacovigilance-system-manual_en.pdf

conditions, complementing prelicensure evaluation with long-term safety evidence. These systems operate at multiple levels (i.e., local, national, regional, and international), and depend on coordinated contributions from healthcare professionals, regulatory authorities, pharmaceutical manufacturers, and patients themselves. The World Health Organization (WHO) defines pharmacovigilance systems as the **national organizational arrangement and technical capacity required to meet a country's pharmacovigilance obligations, with the ultimate objective of maintaining a favorable risk–benefit balance for all authorized medicinal products**.

10.3.1. The WHO Programme for International Drug Monitoring

The **WHO Programme for International Drug Monitoring (PIDM)** represents the cornerstone of global pharmacovigilance and is the coordinating **framework through which countries collaborate to monitor the safety of medicines used worldwide**. Established in 1968 following World Health Assembly Resolution 16.36 (1963), the program emerged as a direct response to the thalidomide disaster, which exposed the need for systematic post-marketing surveillance of adverse drug reactions (ADRs).

The PIDM creates a **global network connecting national pharmacovigilance centers** from WHO Member States. Each participating country collects **Individual Case Safety Reports (ICSRs)**, structured records describing suspected ADRs, and submits them to the WHO global database known as **VigiBase**, which is maintained by the Uppsala Monitoring Centre (UMC) in Sweden, the WHO Collaborating Centre for International Drug Monitoring. As of 2024, VigiBase contains over 35 million reports, making it the world's largest repository of post-marketing drug safety data.

Beyond **VigiBase**, WHO and the UMC operate **VigiAccess**, an open-access web portal allowing the public to view summarized ADR data from the global database. This initiative promotes transparency and encourages community engagement in drug safety monitoring.

Today, the WHO PIDM includes more than 150 full member countries and over 20 associate members, together covering nearly all populations globally. Through this collaboration, the PIDM enhances the detection of rare and serious adverse reactions, strengthens regulatory decision-making, and fosters a culture of shared responsibility for patient safety that transcends national borders.

10.3.2. The EudraVigilance System

EudraVigilance is the European Union's central pharmacovigilance database and information system for managing reports of suspected adverse drug reactions (ADRs) to medicines authorized or under clinical investigation within the European Economic Area (EEA). It was established in 2001 and is administered by the European Medicines Agency (EMA) on behalf of the EU regulatory network.

The system was created to ensure the electronic exchange, evaluation, and monitoring of Individual Case Safety Reports (ICSRs) between marketing authorization holders (MAHs), national competent authorities (NCAs), sponsors of clinical trials, and the EMA in accordance with EU pharmacovigilance legislation, notably Regulation (EC) No 726/2004, Directive 2001/83/EC, and the EU Clinical Trials Regulation (EU) 536/2014.

EudraVigilance comprises two primary operational modules:

- The EudraVigilance Clinical Trial Module (EVCTM), which processes Suspected Unexpected Serious Adverse Reactions (SUSARs) reported during interventional clinical trials; and
- The EudraVigilance Post-Authorisation Module (EVPM), which captures both serious and non-serious ADRs occurring during the post-marketing phase, drawn from spontaneous reporting, literature sources, non-interventional studies, and other real-world evidence streams.

Data submitted to EudraVigilance are coded using standard terminologies such as the **Medical Dictionary for Regulatory Activities (MedDRA)** and comply with the ICH E2B(R3) technical format for electronic case-report exchange. The system's automated safety-message architecture enables efficient routing of ICSRs among Member States, the EMA, and, where applicable, the WHO Uppsala Monitoring Centre (UMC).

Central to EudraVigilance's function is the early detection of new or changing safety signals through ongoing statistical monitoring and pattern analysis. Safety signals emerging from the system are reviewed by the **Pharmacovigilance Risk Assessment Committee (PRAC)**, which may recommend regulatory actions such as label updates, risk minimization measures, or product withdrawals.

Anonymized data from EudraVigilance are made publicly accessible through the European Database of Suspected Adverse Drug Reaction Reports (ADRreports.eu), allowing transparency and public trust in EU medicines oversight. Overall, EudraVigilance exemplifies the integration of national vigilance activities into a coordinated regional network, reinforcing medicine safety governance across the European Union.

10.3.3. The Portuguese Pharmacovigilance System

The **Portuguese National Pharmacovigilance System (Sistema Nacional de Farmacovigilância,** SNF) was formally established in 1992 and is coordinated by the National Authority of Medicines and Health Products, I.P. (INFARMED), the national competent authority responsible for the regulation, evaluation, and surveillance of medicines in Portugal. The SNF **operates within both the European pharmacovigilance framework and the WHO Programme for International Drug Monitoring**, ensuring the collection, assessment, and communication of data on adverse drug reactions (ADRs) from healthcare professionals, patients, and marketing authorization holders.

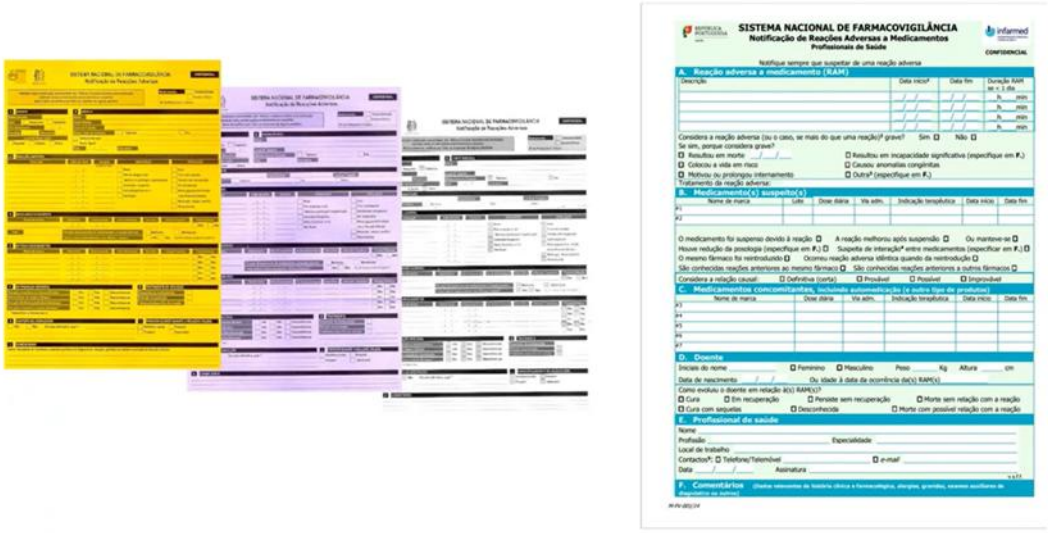
Originally centralized in Lisbon, the system became decentralized in 2000 with the creation of four **regional pharmacovigilance units**, located in the North, Centre, Lisbon and Tagus Valley, and South[7]. Subsequent reforms expanded this structure to improve proximity to healthcare institutions and public reporting. By 2017, the network comprised seven regional units, including those in the Algarve, Azores, and Madeira, integrated with universities and hospitals to enhance scientific capacity and clinical outreach.

Each regional pharmacovigilance unit is responsible for the collection, validation, and assessment of ADRs reported within its geographical area. Reports are routinely entered into the EudraVigilance database and into INFARMED's national portal, ensuring both European and national visibility of safety data. The Medicines Risk Management Department (DGRM) at

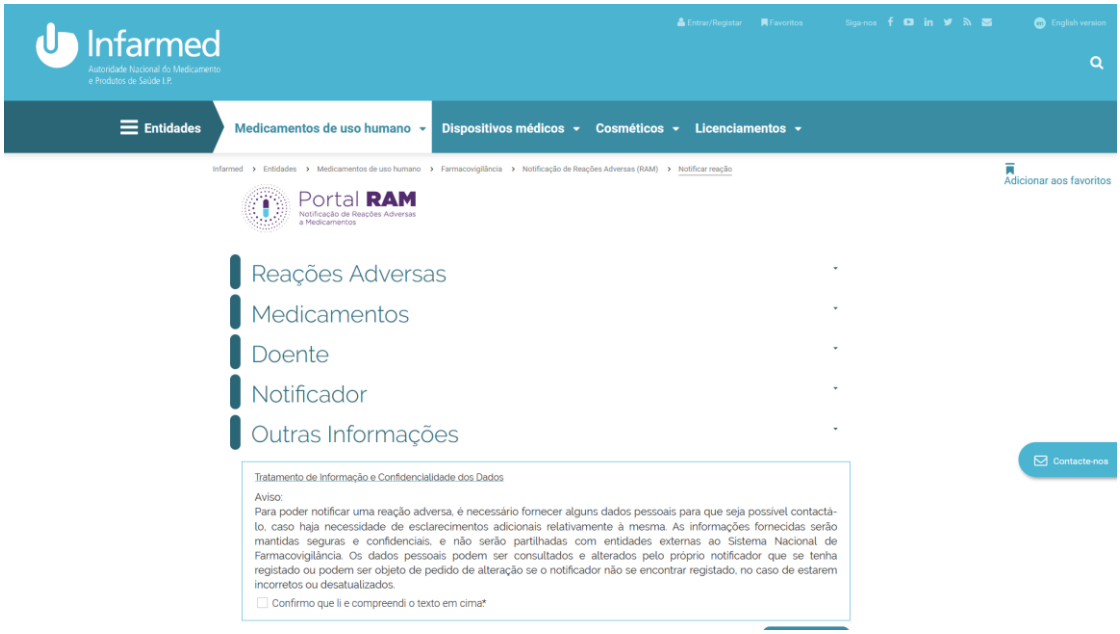
[7] Herdeiro MT, Ferreira M, Ribeiro-Vaz I, Junqueira Polónia J, Costa-Pereira A. O Sistema Português de Farmacovigilância. Acta Med Port. 2012;25(4):241-249.

INFARMED coordinates the system, performs advanced signal detection, and supports decision-making processes in collaboration with the EMA Pharmacovigilance Risk Assessment Committee (PRAC).

Since 2012, **patients and consumers in Portugal have been able to report ADRs** directly via an online portal or dedicated mobile applications (**Portal RAM**[8] and INFARMED App), marking an important step toward participatory pharmacovigilance. INFARMED also publishes a Pharmacovigilance Bulletin, disseminating safety alerts, risk minimization measures, and regulatory updates to professionals and the public alike.



Previous ADR reporting instruments in Portugal



Portal RAM, Infarmed.

[8] Infarmed. Portal RAM. https://www.infarmed.pt/web/infarmed/portalram

10.3.5. The pathway of a spontaneous ADR report

Spontaneous reporting is the core of pharmacovigilance systems and constitutes the first step for recognizing new or unexpected adverse drug reactions (ADRs) once a medicine is introduced into clinical use. The process begins at the individual level and culminates in global data consolidation at the World Health Organization (WHO) through **multiple interconnected systems** that ensure quality review, standardization, and continuous signal detection across jurisdictions.

The process originates when a **healthcare professional or a patient identifies a potential ADR and decides to report it**. In Portugal, this can occur through several channels: directly to the INFARMED Portal RAM, or by contacting a regional pharmacovigilance unit. Reports can also be submitted in paper form or via institutions such as hospitals and community pharmacies that maintain internal ADR monitoring protocols. **The only prerequisite for submission is suspicion; causality does not have to be proven.** A valid spontaneous report requires **four minimum elements: an identifiable patient, a reporter, a suspected drug, and a suspected reaction**. These submissions form the earliest link in an increasingly structured data chain.

Once received, the report enters the regional level, where it is handled by the corresponding **regional pharmacovigilance unit**. The regional teams conduct an initial quality control of the submitted data, **seeking clarifications when necessary**. They perform a clinical validation and a **causality assessment**, often following the WHO–UMC system for standardized case causality evaluation, to determine the likelihood that the reported drug genuinely contributed to the adverse event. The event description and drug identifiers are standardized using the **Medical Dictionary for Regulatory Activities (MedDRA)** to enable international interoperability. The regional unit then transmits validated cases to INFARMED, I.P., the national authority responsible for the coordination and supervision of pharmacovigilance activities.

At the national level, **INFARMED's Medicines Risk Management Department** (DGRM) **aggregates** and analyses all validated reports from across the Portuguese network. These reports are stored in the national pharmacovigilance database and converted into **Individual Case Safety Reports** (ICSRs) structured according to the International Council for Harmonisation (ICH) E2B(R3) electronic reporting format. In addition to data consolidation, national pharmacovigilance officers **assess the seriousness** of each case, identify potential safety signals, and generate synopsis assessments for regulatory review. If a pattern of concern emerges (e.g., repeated reports of a rare adverse reaction linked to a new therapy), Infarmed triggers a national safety evaluation and, if appropriate, referral to the European Medicines Agency (EMA) through routine electronic communication channels.

The **Portuguese system is fully integrated into the European EudraVigilance database**, managed by the EMA. Here, all **incoming national** and **industry-submitted ICSRs** are organized within two operational modules: the Post-Authorization Module (EVPM) for marketed drugs and the Clinical Trial Module (EVCTM) for investigational products. Within EudraVigilance, automated algorithms **continuously scan for disproportionate reporting**, producing statistical indicators such as the **reporting odds ratio (ROR)** that help identify emerging safety signals across the European Economic Area. These signals are further evaluated by the **Pharmacovigilance Risk Assessment Committee (PRAC)**, which determines the need for regulatory measures, such as label updates, warnings, or, in critical cases, market withdrawal.

Validated European cases are then transferred to the WHO Programme for International Drug Monitoring (PIDM), coordinated by the Uppsala Monitoring Centre (UMC) in Sweden. This

transfer occurs through structured data exchange protocols between the EMA and the WHO, ensuring that each country's contributions feed into VigiBase.

Thus, **a spontaneous case submitted by a Portuguese pharmacist or physician may ultimately inform international regulatory action**. When signals are confirmed, **feedback flows downward** through the same institutional hierarchy: the Uppsala Monitoring Centre alerts the WHO and participating national centers; the EMA and PRAC communicate European-level assessments; and INFARMED disseminates updates through its Pharmacovigilance Bulletin and national safety communications.

10.3.6. The Medical Dictionary for Regulatory Activities (MedDRA)

The **Medical Dictionary for Regulatory Activities (MedDRA)** is the global standardized terminology that underpins modern pharmacovigilance and clinical safety communication across all the pharmacovigilance systems described in the previous section. Developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in the 1990s, MedDRA provides a **unified multilingual vocabulary for describing adverse events, medical histories, indications, and procedures throughout a product's lifecycle**.

MedDRA forms the linguistic foundation that allows patient-level safety data to be aggregated, analyzed, and compared across national and international systems. When a spontaneous report enters a regional pharmacovigilance unit, the **narrative description supplied by the reporter** is converted into **standardized medical terminology through MedDRA coding**. This translation ensures that diverse expressions such as "feeling faint," "syncope," and "lost consciousness" are all indexed under a single preferred medical concept, enabling harmonized signal detection in databases such as EudraVigilance and the WHO VigiBase network.

MedDRA's structure is hierarchical and multi-axial, comprising **five interconnected levels**, each providing a different degree of medical specificity:

- **System Organ Class (SOC)**: Represents the broadest level of classification, grouping terms by physiological system, etiology, or medical purpose.

  Examples: Cardiac disorders, Immune system disorders, Infections and infestations.

- **High Level Group Term (HLGT)**: Subordinate to SOCs, HLGTs organize adverse events by related pathophysiological or anatomical aspects, linking clinically similar high-level terms.

  Example: Cardiac arrhythmias under Cardiac disorders.

- **High Level Term (HLT)**: Groups of clinically related adverse conditions nested under an HLGT.

  Example: Supraventricular arrhythmias and Ventricular arrhythmias and cardiac arrest are HLTs within the HLGT Cardiac arrhythmias.

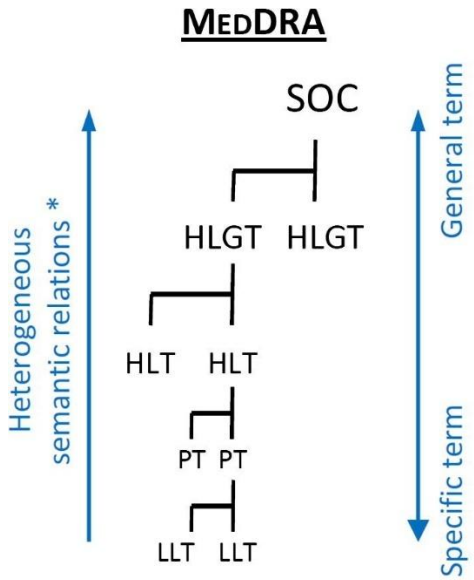
- **Preferred Term (PT)**: Distinct, medically precise descriptors used for coding and analysis. Each PT represents a single unique concept and serves as the primary analytical unit for pharmacovigilance systems.

  Examples: Myocardial infarction, Nausea, Rash.

- **Lowest Level Term (LLT)**: The most specific expressions used in source data, including synonyms, spelling variants, and colloquial terms. LLTs roll up directly to their corresponding PTs, ensuring data consistency during coding.

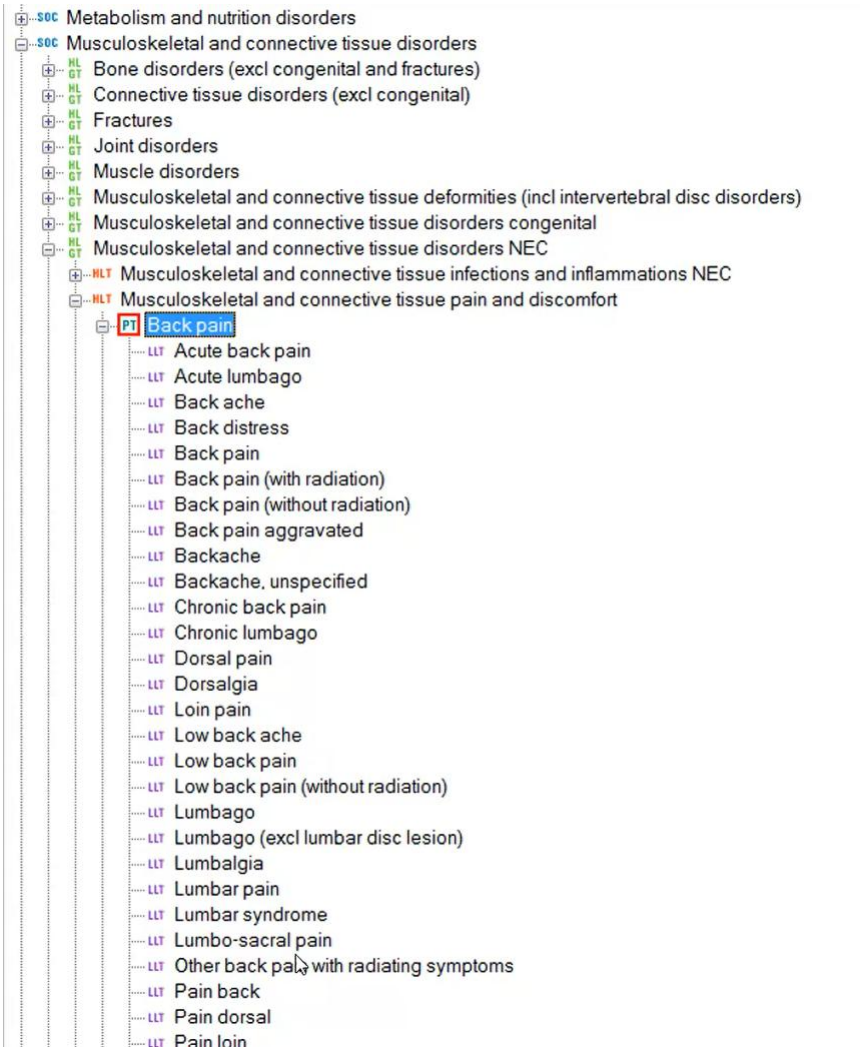
  Examples: “Heart attack” → PT Myocardial infarction, “Feeling queasy” → PT Nausea.

An important feature of MedDRA is its **multi-axiality**, which allows a single term to appear in more than one SOC when clinically relevant. For instance, Hemorrhagic stroke is classified under both Nervous system disorders (by site of manifestation) and Vascular disorders (by pathogenesis). This flexibility enhances data retrieval and aligns with the multidisciplinary nature of adverse event interpretation. The hierarchical relationships are pre-defined in the dictionary, ensuring consistency and reproducibility across institutions and regulatory bodies.



MsdDRA structure[9].

[9] Bousquet C, Sadou É, Souvignet J, Jaulent MC, Declerck G. Formalizing MedDRA to support semantic reasoning on adverse drug reaction terms. J Biomed Inform. 2014;49:282-291. doi:10.1016/j.jbi.2014.03.012



Example of MedDRA vocabulary.

10.4. Causality assessment

Causality assessment is a structured process used to evaluate the likelihood that a reported adverse event has been caused by a particular medicine. While spontaneous reports provide the initial indication of a potential safety concern, causality assessment helps distinguish coincidental medical occurrences from genuine adverse drug reactions. Over time, several standardized tools have been developed to bring consistency and transparency to this process.

WHO–UMC System for Standardised Case Causality Assessment: Developed by the World Health Organization (WHO) and the Uppsala Monitoring Centre (UMC), this globally adopted method provides a qualitative framework relying on clinical and pharmacological evidence. It classifies ADRs into six categories:

- Certain: A clear temporal relationship, positive dechallenge and rechallenge, and absence of alternative explanations.
- Probable/Likely: Reasonable temporal sequence, dechallenge supportive, and no plausible alternative causes, though rechallenge may be lacking.

- Possible: Temporal relationship present, but other factors (e.g., disease, other drugs) could explain the event.
- Unlikely: Time relationship improbable or presence of stronger alternative explanations.
- Conditional/Unclassified: Report incomplete or awaiting further data.
- Unassessable/Unclassifiable: Insufficient documentation prevents judgment.

This system emphasizes clinical reasoning and documentation quality over numerical scoring, and it is the approach used in national pharmacovigilance centres such as INFARMED and the WHO International Drug Monitoring Programme.

Naranjo Algorithm (ADR Probability Scale): The Naranjo Scale, developed in 1981 by Naranjo and colleagues, is one of the most widely used structured questionnaires for ADR causality assessment. It includes 10 questions, each answered as Yes, No, or Do not know, with assigned point values (–1, 0, +1, or +2). The total score defines causality categories:

- Definite: ≥9 points
- Probable: 5–8 points
- Possible: 1–4 points
- Doubtful: ≤0 points

Questions assess key elements such as the timing of the event relative to drug exposure, improvement after **withdrawal** (dechallenge), recurrence on **re-exposure** (rechallenge), presence of alternative causes, and previous patient experience with the drug. Its simplicity allows reproducibility, though it may oversimplify complex clinical cases.

Bayesian and probabilistic approaches: Some modern methods use Bayesian statistics or probabilistic models to estimate the likelihood of drug causation. These include the Bayesian Adverse Reactions Diagnostic Instrument (BARDI) and other probabilistic causality models that apply conditional probability to evaluate association strength. Such methods are particularly relevant when large databases, such as EudraVigilance or VigiBase, are analyzed automatically to detect disproportionate reporting patterns. They allow continuous quantitative updating as new cases accumulate, enhancing objectivity for large-scale data but requiring substantial computational capacity and statistical expertise.

Other algorithmic tools: Several national pharmacovigilance programs have developed their own algorithms tailored to their data needs:

- The French method (Begaud algorithm), combining chronological, semiological, and bibliographic criteria.
- The Kramer algorithm, which evaluates causality when multiple drugs are suspected.
- The Liverpool ADR Causality Assessment Tool, designed for hospital clinical use.

Despite their differences, all share the same core principles—temporal plausibility, biological plausibility, reversibility, exclusion of alternative causes, and reproducibility.

Expert judgement and hybrid evaluations: In complex or ambiguous reports, algorithmic approaches are often supplemented by expert judgement. Panels typically include clinicians, pharmacologists, and toxicologists who review the totality of the evidence. Expert committees provide contextual insights that algorithms may miss, ensuring clinical realism in regulatory decision-making.

10.5. Signal Detection

Signal detection is the process of identifying new or changing safety information concerning medicinal products, transforming cumulative adverse drug reaction (ADR) data into potential signals of harm that deserve further clinical or regulatory evaluation. A signal is defined by the World Health Organization (WHO) as "**reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously**". Once causality is assessed at the level of individual case safety reports (ICSRs), signal detection integrates thousands of such reports to uncover population-level risk patterns that may not be visible from isolated observations.

Signal detection aims to identify early indications of new adverse effects, or significant shifts in known risks, using data sourced primarily from spontaneous reporting systems, such as EudraVigilance and VigiBase. Complementary sources include literature, observational studies, clinical trial data, and electronic health record linkages. The process operates in a cyclical framework, encompassing five sequential stages: detection, validation, prioritization, assessment, and communication. This flow is mandated under EMA's Good Pharmacovigilance Practices (GVP) Module IX, which defines the principles for EU-wide signal management[10].

In traditional signal detection, two complementary methods—qualitative and quantitative—are employed:

- **Qualitative detection** relies on expert review. Pharmacovigilance assessors examine case series within ICSRs, looking for coherent patterns such as temporal relationships, rechallenge evidence, or clustering among specific demographics. Though resource-intensive, qualitative evaluation remains indispensable for rare, serious, or mechanistically complex reactions.
- **Quantitative detection** uses statistical algorithms to assess disproportionate reporting frequencies of drug–event pairs in large databases. The assumption is that if an ADR is genuinely associated with a drug, that pair will appear more often than expected relative to all reports. These numerical methods enable efficient, systematic monitoring of massive datasets.

A range of recognized algorithms are employed globally across regulatory databases. Each expresses the same conceptual principle, identifying disproportionality between observed and expected reporting patterns, but differs in its computation and statistical distribution[11]:

Proportional Reporting Ratio (PRR): Used by the European Medicines Agency (EMA) and integrated into EudraVigilance, PRR calculates the ratio between the proportion of a specific ADR for a drug and the proportion for all other drugs. A signal is flagged when the PRR exceeds a threshold (commonly ≥2) and the associated chi-square test indicates statistical significance.

[10] EMA. Guideline on good pharmacovigilance practices: Module IX, Signal management. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf

[11] Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427-436. doi:10.1002/pds.1742

	Adverse event (Y)	Not adverse event (Y)	Total
Using drug X	a	b	$(a+b)$
Not using drug X	c	d	$(c+d)$
Total	$(a+c)$	$(b+d)$	$(a+b+c+d)$

$$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$$

Reporting Odds Ratio (ROR): Applied widely by national pharmacovigilance centers, ROR quantifies the odds of an event occurring with one drug compared to all others. Preferred for hypothesis generation, it provides intuitive odds-based interpretation[12].

$$\mathrm{ROR} = \frac{a/b}{c/d}$$

And, even clearer, considering that we have only information about the reported ADR:

	Target adverse event	The other adverse events
Drug of interest	n_{11}	n_{12}
The other drugs	n_{21}	n_{22}

$$ROR = \frac{\frac{n_{11}}{n_{12}}}{\frac{n_{21}}{n_{22}}}$$

$$\boldsymbol{PRR} = \frac{\frac{\boldsymbol{n_{11}}}{(\boldsymbol{n_{11}+n_{12}})}}{\frac{\boldsymbol{n_{21}}}{(\boldsymbol{n_{21}+n_{22}})}}$$

Information Component (IC): Developed by the Uppsala Monitoring Centre for the WHO VigiBase, IC is calculated through a Bayesian Confidence Propagation Neural Network (BCPNN). It evaluates the **difference between observed and expected probabilities of drug–event**

[12] Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(8):519-523. doi:10.1002/pds.1001

combinations, adjusting for uncertainty and small-sample variability. A positive IC value exceeding the credibility interval threshold constitutes a statistical signal.

Empirical Bayes Geometric Mean (EBGM): Utilized primarily in the FDA Adverse Event Reporting System (FAERS), this Bayesian model smooths disproportionality estimates by incorporating prior probability distributions, enhancing stability in sparse data environments.

Together, these algorithms operate as filters that flag associations warranting clinical scrutiny, not as proof of causality. Once detected, potential signals undergo human validation by pharmacovigilance experts to exclude artefacts such as duplicate reports, confounders, or class effects.

Recent advances in **artificial intelligence (AI)** are reshaping signal detection. Studies demonstrate that machine learning models, including random forests, gradient boosting machines, and k-means clustering algorithms, can outperform traditional disproportionality metrics in predictive accuracy while supporting automatic triaging of safety signals in real time. Natural language processing (NLP) algorithms increasingly assist in extracting ADR information from free-text clinical narratives or social media sources, complementing structured regulatory data. Ensuring transparency, reproducibility, and regulatory interpretability remains central to their validated implementation.