EUDRAVIGILANCE DATABASE: REPORTING AND SIGNAL DETECTION PROCESS

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Abstract

The EudraVigilance system, developed and managed by the European Medicines Agency (EMA), is a centralized database for monitoring the safety of medicinal products within the European Economic Area (EEA). It plays a crucial role in pharmacovigilance by facilitating the collection, management, and analysis of suspected adverse drug reactions (ADRs) through Individual Case Safety Reports (ICSRs). These reports are submitted by healthcare professionals, patients, and pharmaceutical companies in a standardized electronic format based on guidelines from the International Council for Harmonisation. The reporting process involves identification of ADRs, preparation and submission of ICSRs, followed by validation and coding using standardized terminologies such as MedDRA. High-quality data are essential for effective signal detection, which aims to identify new or previously unrecognized associations between drugs and adverse events. Signal detection in EudraVigilance utilizes statistical methods such as proportional reporting ratios and reporting odds ratios, combined with expert clinical evaluation to ensure accuracy and relevance.

The system supports a structured signal management process, including signal identification, validation, prioritization, and assessment. Regulatory authorities, particularly the Pharmacovigilance Risk Assessment Committee (PRAC), evaluate validated signals and recommend appropriate actions such as updating product information, issuing safety warnings, or restricting drug use. Despite its effectiveness, EudraVigilance faces challenges such as underreporting, data quality variability, and difficulties in establishing causality. However, ongoing advancements in technology, including the use of artificial intelligence and improved data transparency, are enhancing its performance. In conclusion, EudraVigilance is a vital tool for ensuring drug safety, enabling early detection of risks and supporting evidence-based regulatory decisions to protect public health.

Keywords

EudraVigilance; Pharmacovigilance; ReportingProcess; SignalDetection; Adverse Drug Reaction (ADRs); Individual Case Safety Reports (ICSRs); European Medicines Agency (EMA); International Council for Harmonisation (ICH); Data Validation; MedDRA Coding; Signal Management; Drug Safety Monitoring; Risk–Benefit Assessment; Post-marketing Surveillance;

Pharmacovigilance

introduction

Pharmacovigilance, defined by the World Health Organization (WHO) as “the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drugrelated problems,” plays a vital role in ensuring drug safety across healthcare systems worldwide [1]. This discipline was initially established following significant public health crises, most notably the thalidomide tragedy in the 1960s, which underscored the need for systematic drug safety monitoring [2]. The catastrophic effects of thalidomide, primarily used as a sedative in pregnant women, led to thousands of congenital disabilities, ultimately sparking

regulatory changes that laid the foundation for modern pharmacovigilance practices [3]. Pharmacovigilance not only focuses on adverse drug reactions (ADRs) but also encompasses broader risk management, which includes tracking, evaluating, and mitigating risks associated with medicinal products. Given the complex landscape of drug safety, pharmacovigilance now involves an interdisciplinary approach, including clinical pharmacy, regulatory science, epidemiology, and data analytics [5]. The goal is to enhance patient safety by continuously assessing the risk-benefit profile of medicinal products as they are developed, tested, approved, and made available in real-world settings [5] With the expansion of pharmacovigilance efforts, several methodologies have been adopted, including spontaneous reporting systems, cohort and casecontrol studies, and automated database systems. These tools have transformed pharmacovigilance into a proactive science, helping detect drug-related risks early and informing safer clinical practices [6]. Moreover, regulatory bodies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and the WHO have developed stringent guidelines and frameworks to oversee pharmacovigilance activities, highlighting the importance of harmonized drug safety standards across countries [7]. In recent years, the scope of pharmacovigilance has expanded, particularly with advances in digital health technologies and artificial intelligence (AI), which have increased the capacity to monitor and analyze ADRs from vast amounts of data more effectively. These advancements have enabled a shift toward real-time pharmacovigilance, allowing healthcare providers and regulatory agencies to react promptly to potential safety signals [8]. The ongoing evolution in this field underscores the necessity of integrating modern tools with established practices to create a robust pharmacovigilance system that meets contemporary drug safety challenges

The Impact Of Pharmacovigilance On Adverse Drug Reactions

More than 100,000 people died in 1994 as a result of undesirable medication reactions. Additionally, from 1999 to 2008, 26,399 fatalities and 0.9% of emergency hospital admissions were attributable to adverse drug responses, indicating that these reactions are to blame for significant proportion of morbidity and mortality among patients [9]. Despite different prevention measures, research indi cates that between 5% and 10% of patients may experience an adverse drug reaction (ADR) upon admission or during hospitalization. PV has a profound effect on the frequency of occurrence of ADRs. PV has considerably decreased the frequency and severity of ADRs through systematic data collection, analysis, proactive risk assessment and taking appropriate measures. PV has made quick action and risk reduction possible via early ADR detection, frequently in the post-marketing phase. Continuous real-world data monitoring allows for the detection of new safety signals, which in turn leads to regulatory steps like updated drug labeling, dosage changes, or even the

recall of danger ous drugs. ADRs have been seen to occur less frequently as a result of improved drug labeling and more public awareness, which have given patients and healthcare professionals the power to make wise decisions [10–13]. PV focused its efforts on managing the drug adverse effects through its global central database, which compiles reports of drug side effects from all around the world, in order to combat this phenomenon. The safety profile of the medications, patient care, and safety are all significantly improved by this position, which also supports the efforts of national drug regulatory agencies [14].

Importance Of Pharmacovigilance

There are still a lot of unanswered questions regarding the safety profile of new pharmaceuticals when they are first brought to the market. These drugs are used by a variety of patients for a variety of illnesses. These patients may also be taking other medications, and they must adhere to various customs and dietary restrictions, all of which could have a negative impact on how well the treat ments work. Additionally, different formulations and components within the same drug are pos sible. While taking medications with conventional and herbal treatments, ADRs may also occur and need to be watched for using PV. A certain medication's ADRs may occasionally exclusively happen in one nation or region. PV is a crucial monitoring system for the safety profile of medica tions in a nation, with the cooperation of doctors, chemists, nurses, and other health professionals of the country. It aims to prevent any unnecessary physical, mental, and financial suffering of patients [15]. Besides patient safety, PV has an important role in the following areas.

Eudravigilance

Introduction

EudraVigilance (EV) is the system for collecting, managing and analysing suspected adverse drug reactions (ADRs) to medicines authorised in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system, which became operational in December 2001, on behalf of the European Union (EU) medicines regulatory network [16]. On 4 February, 2016, 15 years after the pharmacovigilance database was launched, submissions to EV reached 10 million individual case safety reports (ICSRs), making it one of the biggest spontaneous reporting systems in the world. This milestone coincided in time with significant technical enhancements and with a major revision of the EV access policy aimed at increasing the utility and accessibility of the ICSR data in line with the pharmacovigilance legislative requirements [17-19], and thereby at further contributing to public health protection. Since November 2005, the electronic reporting of suspected ADRs is mandatory in the EEA [17-18]. The submission of ADRs from both marketed use and from trials is based on the standards agreed at the level of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [20] and the International Organization for Standardization [21], which allow for a structured and standardised way safety information is to be collected and exchanged. By the end of 2017, EV held a total of 12,451,826 ICSRs, referring to 7,948,873 individual cases (one case can relate to more than one ICSR owing to follow-up information supplementing and updating initial reports). In total, 402,690 cases were submitted from interventional clinical trials and 7,546,183 from the post-authorisation setting of the medicinal products. Of the cases submitted from post-authorisation, 64% (4,838,460) were submitted from outside the EEA and 36% (2,707,723) from EEA countries. During the course of 2017 alone, 1,076,811 individual cases were transmitted from post-authorisation, 418,383 from EEA countries. Of those, 84,372 were directly submitted by European patients and consumers through national competent authorities (NCAs) in the Member States and marketing authorisation holders (MAHs). The EEA country distribution of patients' reports analysed by Banovac et al. in 2017 [22] showed that the highest number of reports originated from the Netherlands, followed by the UK, Germany, France and Italy. The same five countries contributed 77% of all healthcare professional reports to EV. In May 2017, following a period of technical development, guideline updates, engagement with the stakeholders and an independent system audit, the EMA Management Board announced that the EV database has achieved full functionality [23]. This

triggered the application of both the simplified reporting rules for NCAs and MAHs and the extended access to the database with the goal to further support the safety surveillance of medicinal products in the EU, increase transparency and enable greater use of the data by stakeholders, including researchers.

Use of EudraVigilance Data

In this section, we review the use of EV data up to December 2016, including published reviews, with the aim to provide an overview of their use for health research. The launch of the enhanced system functionalities and the new access to data provide the research and medicine safety communities with the opportunity to make a much greater use of this data source, and this review therefore serves both as an inspiration and a challenge. Use of EV data by the EU regulatory network includes a summary of areas such as signal detection and evaluation, PSUR assessments [24] and referrals. During 2017, the number of signals prioritised and analysed by the Pharmacovigilance Risk Assessment Committee was 82 and overall, the source of 63% included data from EV. In addition to the use of EV by the EU regulatory network, other groups such as healthcare professionals and patients can obtain information on ADR data submitted to EV via the 'European Database of Suspected Adverse Drug Reactions Reports' [25] (hereinafter referred to as the 'ADR website'). This information is available from the EMA website with guidance on the interpretation of the

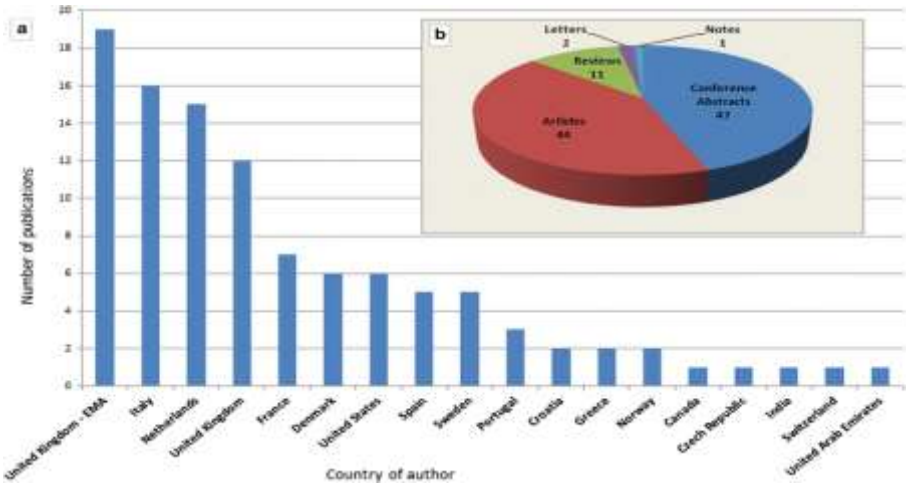

Fig. 2 Publications using **EudraVigilance** data up to 31 December, 2016, classified per country of author and type of publication (as per the classification stated in EMBASE). Absolute numbers. EMA European Medicines Agency

data. In 2017, the ADR website registered an average of 17,068 visits per month.To have an overview about how EV data has been used in research and scientific publications, a search in EMBASE [26], PubMed and PubMed Central [27] was conducted using specific keywords [see the Electronic Supplementary Material (ESM)]. This provides an illustration of the use of the data with the aim of informing researchers about how EV can be used. The search included publications up to 31 December, 2016 and retrieved methodologies (e.g. signal detections methodologies, pharmacovigilance in paediatric population) or ADR reporting patterns (e.g. consumer reports, medication errors); and (3) 'clinical perspectives' when the EV data were used to support clinical practice and treatment guidance discussions. Figure 3 shows the citations distributed by year of publication (a) and the main classification of the publications (b). Within the time distribution, there is a marked increase after 2012–2013 probably driven by the implementation of the 2010 pharmacovigilance legislation and the increased accessibility of the data, including through the release of the public ADR website [28]. Together with the EV data, the publications are supported by other sources of information. These include spontaneous reporting systems such as the World Health Organization (WHO) global database of individual case safety reports (VigiBase) [29], the US Vaccine Adverse Event Reporting System [30], the US FDA Adverse Event Reporting System [31], NCAs databases and safety data- bases from MAHs. Furthermore, data

is provided from electronic health records databases, health insurance companies, legal datasets and patient registries. In 63% of the

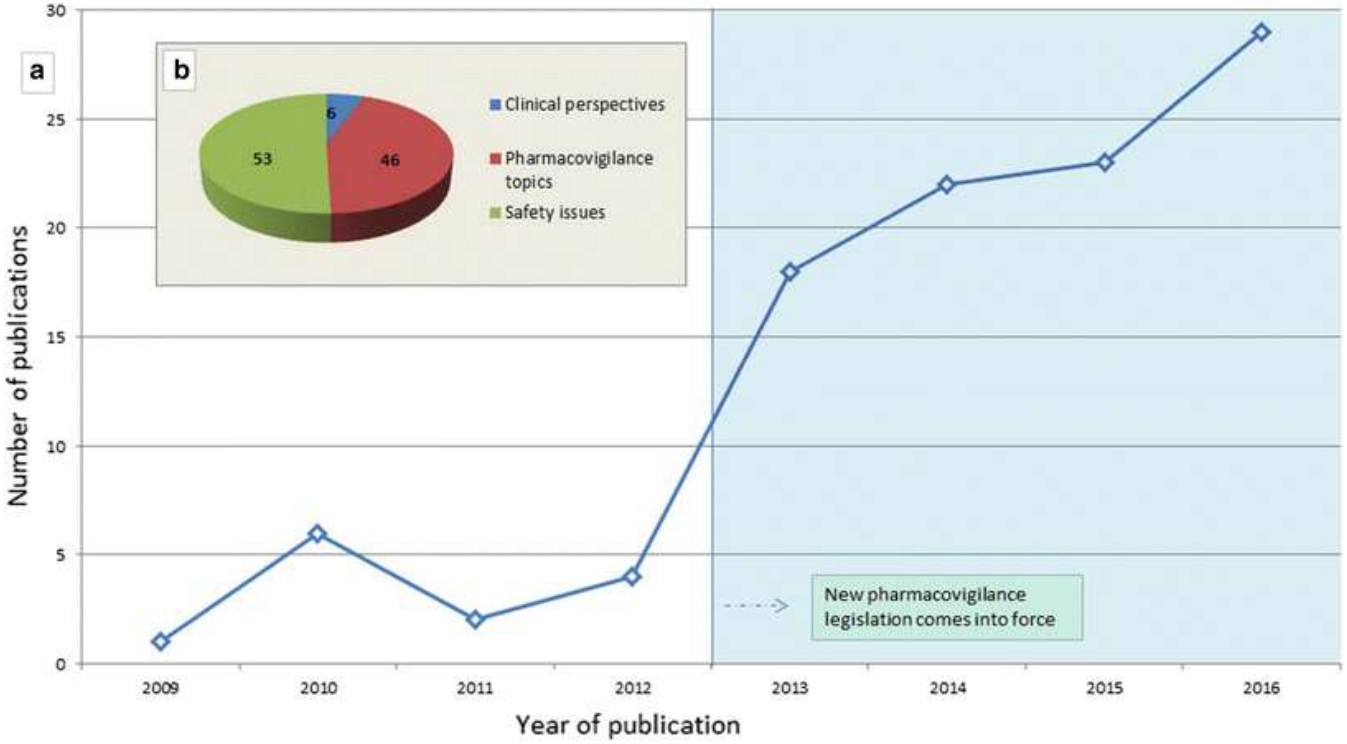

Fig. 3 Publications per year and the main classification of the publications using EudraVigilance data up to 31 December, 2016. Absolute numbers

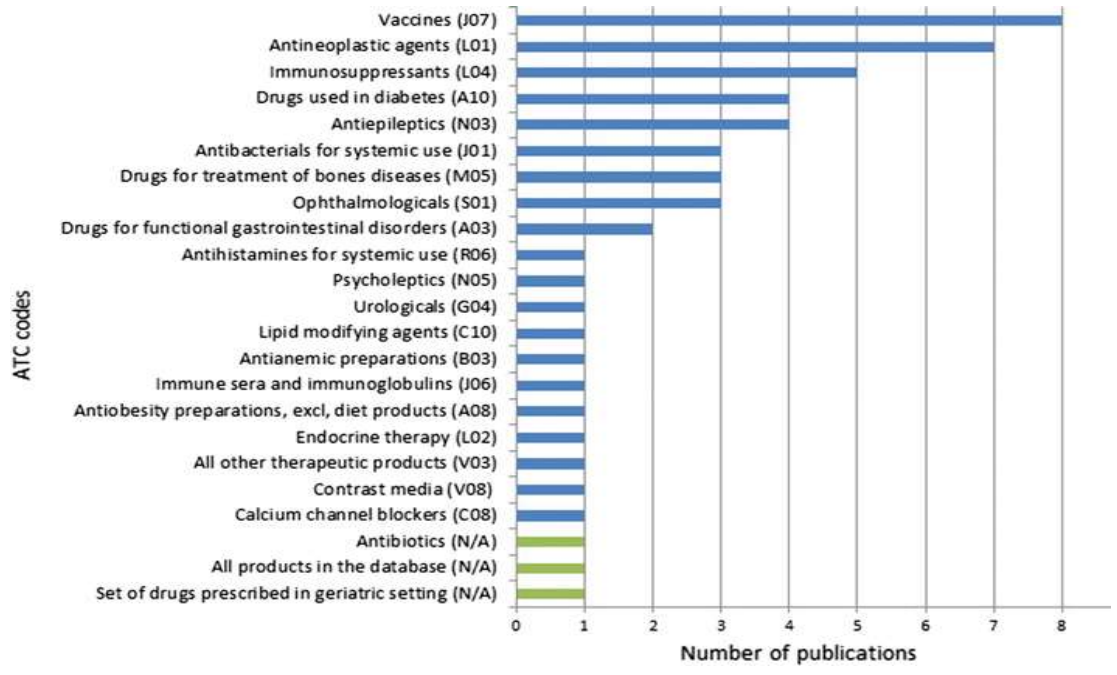

Fig. 4 Anatomical Therapeutic Chemical (ATC) code classification of the drugs analysed in the publications using EudraVigilance data to describe safety issues up to 31 December, 2016. Absolute numbers. excl excluding.

publications retrieved, EV is the sole spontaneous reporting system used for the research. The specific drug-related safety issues are summarised in the ESM for this article including the drugs involved and the databases used for the analysis. The classification of drugs for which data are analysed in the 53 (50%) publications related to safety issues shows interests in a wide range of therapeutic areas, from medications administered presumably to relatively healthy populations, such as vaccines, to antineoplastic agents used in patients affected by a significant disease burden. Figure 4 provides the classification of the drugs analysed in these publications classified by Anatomical Therapeutic Chemical code [32] with the exception of the last three sets of drugs ('drugs prescribed in geriatric setting', 'antibiotics' and 'all products in the database') that cannot be allocated to a specific Anatomical Therapeutic Chemical code. provides the MedDRAÒ System Organ Classes of the 53 publications describing safety issues with the exception of the 11 publications aimed at characterising the entire safety profile of the drugs. Two publications are allocated to two different System Organ Classes. 46 (44%) publications describing general pharmacovigilance topics contain research to analyse methodologies, especially on statistical signal detection, together with descriptions of specific situations that should to be taken into consideration when analysing safety data (e.g. paediatric population or ADR reports from consumers). The category related to signal detection methods includes publications under the scope of the IMI PROTECT project for which public funding was allocated [33-35].

provides the classification of the pharmacovigilance topics yielded by the literature search. One of the first publications on signal detection methods in EV refers to the validation study performed by the EMA to quantify the benefit that can be obtained by adding signal detection using the proportional reporting ratio to established pharmacovigilance methods. The study determined that statistical analysis has the potential to provide significant early warning on adverse reactions to medicines [36]. Since then, 22 other publications have used EV data to investigate signal detection methods. Choosing the thresholds, comparison of disproportionality measures, development of a score for the prioritisation of torsadogenic signals and analysis of variables that could influence signal detection in well-established products are among the topics covered. Based largely on the research conducted under the auspices of IMI PROTECT Work package 3 (signal detection) [37] [38,]the EMA announced in 2015 the revision of the guidance of screening for adverse reactions in EV [39]. The final guideline was published in December 2016 [40]. This represents an important example of research-based improvement in regulatory practice. The six publications related to clinical perspectives refer to the use of novel oral anticoagulants, in light of the experience with dabigatran [41], information systems for translational pharmacogenomics [42] and the use of sodium-glucose co-transporter 2 inhibitors with insulin for the treatment of type 2 diabetes [43]

Signal Detection

In pharmacovigilance signal detection is very important process to identify new safety signals with drugs marketed recently or change of the frequency or seriousness of adverse events that are already known to be associated with the drugs and the process of actively searching for and identifying safety signals from a wide variety of data sources. Signal Detection is one of the core steps in monitoring life cycle of medicinal product. As per article 107h of Directive 2001/83/EC, article 28a of Regulation (EC) No 726/2004 and chapter III of Commission Implementing Regulation (EU) No 520/2012 MAH need to do signal management process. (44) Once a new drug gets marketing approval it is important to review reports ICSRs at the case the level for the purposes of signal detection. Thus, proper prioritization thresholds must be put in place to focus attention on groups of ICSRs. There are a unit each descriptive similarly as quantitative way that of achieving prioritization. Adverse drug events should be separated using the MedDRA dictionary to identify signals using different levels of granularity. Preferred Term (PT) level term use in analysis of signal has been shown to have the best combination of sensitivity and positive predictive value for signal detection. Signals can be detected by qualitative and quantitative methods, details information given in table. Different types of adverse events need different methods for signal detection. Signals obtain from spontaneous reports often have in

small numbers of cases are predominantly qualitative in nature. Quantitative signals often contain type B or C adverse reaction and may be found in large safety databases like FDA Adverse Events Reporting System (FAERS), EudraVigilance and VigiBase. Some basic points is important to identified to determine the evidence present in a signal: quantitative strength of the latency, listedness, rechallenge, consistency of data present, exposure response relationship, potentially causal association between event and drug, experimental findings, possible analogies and the data nature, quantity and quality. (45)

Criterion	Explanation
Quantitative	
Strength of the association	The number of case reports (in relation to exposure to the drug), statistical disproportionality and significance
Qualitative	
Consistency of the data	The general presence of a characteristic feature or pattern, and absence or rarity of converse findings
Exposure-response relationship	Site, timing, dosage-response relationship, reversibility
Biological plausibility of the hypothesis	Pharmacological and pathological mechanisms
Experimental Findings	Rechallenge, drug-dependent antibodies, high blood or tissue drug concentrations, abnormal metabolites, diagnostic markers
Analogy	Previous experience with related drugs; event known to frequently be drug-induced
Nature and quality of the data	Characteristic nature and objectivity of the event, accuracy and validity of documentation, case causality assessment

The assessment of ICSRs and literature is important to detect safety signals for marketed drugs. Detection of signal from ICSRs relies on accurate assessment by trained pharmacovigilance professionals. However, statistical, and computational methods have played an important role because day by day databases have grown larger as spontaneous reporting increase. Screening of huge numbers of individual case reports by automated or semiautomated method to identify possible drug safety issues often use by many marketing authorization holders. Adverse drug events caused by drugs are a major impediment to beneficial pharmacological therapy: they may cause mortality and morbidity, and trigger patients to stop otherwise effective treatment. With several necessary risk's unknown at the time of selling, detection of those risks as timely and accurately as doable is of utmost importance of signal detection. (46)

General terminology Signal:

Information arising from one or multiple sources, including observations and experiments, which suggests latest potentially causal association, or novel aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that's judged to be of sufficient likelihood to justify verificatory action. New aspects of a known casual association may include changes in the frequency, distribution (e.g. sex, age group and country of occurrence),duration, severity, or outcome of the adverse reaction. A signal often relates to all or any medicinal products containing an equivalent active substance, including combination products. Certain signals may only be relevant for a specific medicinal product or during a specific indication, strength, pharmaceutical form, or route of administration whereas some signals may apply to a whole class of medicinal products. (47)

Validated signal: A signal for which the signal validation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

Non-validated signal: A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted.

Refuted signal: A validated signal which, following further assessment has been determined to be "false" i.e. a causal association cannot be established at that point in time.

Confirmed signal: A validated signal entered in EPITT that requires further analysis and prioritization by the PRAC, according to the PRAC Rapporteur or (lead) Member State.

Non-confirmed signal: A validated signal entered in EPITT that does not require further analysis and prioritization by the PRAC at that point in time, according to the PRAC Rapporteur or (lead) Member State.

Ongoing Signal: Signal under evaluation at the data lock point of the PSUR/PBRER.

Closed Signal: Signal for which evaluation was completed before the data lock point of the PSUR/PBRER.(48)

Emerging safety issue: A safety issue considered by a marketing authorization holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals. Examples include:

• Major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events.

• Major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contra-indication, a restriction of use of the medicinal product or its withdrawal from the market

• Major safety-related regulatory actions outside the EU, e.g. a restriction of the use of the medicinal product or its suspension. (49)

Designated medical events: Some medical events are known to result on most occasions from exposure to medicines. Thus, when such events are reported, the prior probability of a causal relationship to one of the medicinal products listed in the ICSR is high. Hence the ICSRs will evoke concerns even before an SDR is observed. A list of these terms, complemented by important and serious events that should not be missed, should then be created, and can serve as a safety net in signal detection. It is recommended that these designated medical events (DME) are drawn to the attention of signal detection assessors irrespective of any other statistical methods used and that they are prioritized for clinical review. Elements of the DME list are generally a relatively small subset of the IME list. (50)

Signal Detection Steps: Signals arising from spontaneous reports also could be detected via Monitoring large adverse drug reaction databases such as Eudravigilance and the FDA AERs system, Published articles,

PSURs/PBRERs and Ongoing benefit-risk monitoring. The process for managing signals by MAH and regulatory authorities / must systematically address the following steps:

1. Signal detection
2. Signal validation
3. Signal confirmation
4. Signal analysis
5. Signal prioritisation
6. Signal assessment
7. Recommending action (51)

Signal detection: Signal detection is a process of detecting signal from available data set and involve an assessment of ICSRs, statistical analyses, or a combination of both, depending on the size of the data present. When it's not relevant or possible to assess every individual case (e.g. signals detected from published studies, healthcare record data), assessment of aggregated data should be considered. At the same time expert need to focus on serious and important events, the Important Medical Event (IME) list should be used to assessment and Designated Medical Events (DME) should always be prioritized. In addition, it is important for experts conducting signal detection to have access to a reference safety information (RSI) to check labelling of events. This will help to in validating and assessing a signal is not assess for information that is already present in RSI.

Sources for the detection of signals:

- Spontaneous reporting
- Active monitoring systems
- Interventional studies (clinical trials)
- Non-interventional studies (pharmacoepidemiology studies)
- Non-clinical studies (e.g. animal toxicology studies)
- Published Scientific literature
- Systematic reviews
- Meta-analyses
- Data from in regulatory databases (e.g., FDA Adverse Events Reporting System (FAERS), EudraVigilance and VigiBase)
- Health Authority safety communications
- Post-Authorization Safety Studies (PASS)
- Other relevant sources

Signal validation: The process of evaluating the data to supporting the newly identified signal to verify that the available data contains sufficient evidence demonstrating the existence of a new potentially causal association, or a brand new facet of a well-known association between drug and new signal. The below points should be considered during signal validation based on the review of ICSR data:

- **Previous awareness:** The information on the adverse events is already added in the reference safety information (SmPC, pack insert and package leaflet)The signal relates to an adverse event already added in the SmPC for other products having same active substance. The association has previously been analyzed and added in the RMP and PSUR. □
- **Strength of the evidence**: The strength of evidence of signal evaluated based on number of ICSRs received with temporal association, positive dechallenge or rechallenge, lack of alternative causes, assessed as possibly related, consistency of the evidence across cases, quality of the data and dose-reaction relationship.
- **Clinical relevance and context:** Some sources of information may provide evidence for a causal association, or a new aspect of a known association, and may be considered during further assessment of the signal. It include seriousness and severity, outcome and reversibility of the adverse event, additional insight on a known adverse events, reactions occurring in the context of drug-drug interactions, populations including pregnant women, children and elderly population, events occurring in different patterns of use e.g. overdose, abuse, misuse, off-label use, medication errors.

Signal confirmation: Signal confirmation is the responsibility of the PRAC Rapporteur for CAPs, and the lead Member State. PRAC or lead Member State should confirm signal or not the signal, i.e. decide whether or not it should undergo PRAC analysis and prioritization. Member State or rapporteur may decide not to confirm a validated signal if, signal is already adequately handled through a different procedure (e.g. PSUR, variation), validated signal involves an adverse reaction that is already adequately reflected in the product, signal has already been subject of review and the available data does not warrant additional analysis because of restricted proof or clinical relevancy.

Signal analysis, prioritization and assessment by the PRAC: Once the Agency or the competent authority within the Member State verificatory or confirming a signal considers that imperative action is needed before the subsequent PRAC meeting, it should use the pharmacovigilance rapid alert system of the EU regulatory network to inform this network about the issue and request discussion on any potential action. The PRAC ought to prioritize signals taking into consideration the dataprovided by the Member State or rapporteur that confirmed the signal. The PRAC might any amend the scope of the signal management by extending it to alternative active substances of a similar category of medicative product or to alternative connected adverse reactions. When further assessment is considered needed within the signal procedure, the PRAC should appoint a rapporteur and define a timeframe considering the prioritization of the signal. The appointed rapporteur ought to lead the assessment and transmit to the PRAC an assessment report. The assessment report should include a proposed recommendation and should be updated as appropriate based on comments from other PRAC members and the MAH. Marketing authorization holders shall collaborate with the PRAC for the assessment of the signals by providing the additional information requested. Such requests are generally addressed to marketing authorization holders of the reference medicinal products and usually consist of a cumulative review of relevant data (e.g. from spontaneous reports, clinical trials, scientific literature), together with a discussion and conclusion from the marketing authorization holder. Marketing authorization holders that provide data are also invited to comment on the rapporteur's preliminary assessment report. When the PRAC recommends assessment of the signal among another procedure (e.g. PSUR, referral, variation), the method and timelines for that procedure apply and therefore the signal procedure is closed.

Recommendations on signals from the PRAC: PRAC recommendations are adopted after prioritization and after each plenary discussion during the assessment of the signal. The recommendations may include any or a combination of the conclusions: The MAH should provide additional data for assessment within a signal procedure, review of additional data on the signal in the following PSUR or submit an ad-hoc PSUR, update the reference safety information through an application for a variation, requested to submit an RMP or to update the RMP, implement additional risk minimization measures such as educational materials or the

dissemination of a Direct Healthcare Professional Communication, a post-authorization study according to an agreed protocol and submit the final results of that study. PRAC recommendations to provide additional data are communicated directly to concerned MAH by the Agency.

Signal Detection Methods

Signal detection methods are 'qualitative' as per case-by-case assessment of safety reports and 'quantitative' by means of data mining tools using real-world databases. The qualitative and quantitative assessment is further subjected to validation and confirmation by clinical evaluation and subject expert judgment.

Qualitative Methods

This is a traditional approach, also known as case-by-case analysis of ICSRS, case series, aggregate datasets (periodic safety update reports) and other sources (e.g., published biomedical literature, health authorities, media, internet, social media). Each D-AE combination case is reviewed and thoroughly assessed by medically qualified persons to establish evidence to confirm or reject causal associations. This is followed by systematic evaluation of multiple case reports of D-AE combinations, wherein the cumulative data (number of reports in database in the given time period), frequency trends over time and frequency rates to specific time period, system organ classification and Medical Dictionary for Regulatory Activities (MedDRA) coding with combined retrospective analysis using computerized tools are undertaken. In addition, scientific literature, characteristic of patient population exposed, pharmacological plausibility are evaluated in detail. However, manual assessment of individual reports is time consuming and practically not suitable for large database analyses. This has resulted in the development and application of statistical data mining tools for drug safety surveillance.

Quantitative Methods

The quantitative methods offer unique prospects that leverage to complement or augment existing qualitative approaches. These methods can also detect potential signals for further investigation that are not readily recognizable or apparently evident on a single case report. These are systematic examinations of the reported AEs using statistical or mathematical tools that are quick and detect signals earlier. However, they are primarily useful for large datasets and not suitable for solo ICSR. A recommended minimum database size is 5,000 reports, as a suitable lower limit to avoid excessive rates of false-positive associations. These methods have been valuable to establish the relationship between pioglitazone and bladder cancer, rofecoxib exposure and thrombotic ADRs [52].

Various statistical algorithms are applied to a database to identify drug-AE pairs (or frequent combinations of a drug and an event) that occur with disproportionately high frequency in large spontaneous report databases. Typical methodologies include the disproportionality analysis (DPA) (statistics) or the Empirical Bayesian Geometric Mean (EBGM). The system automatically generates statistical values or scores that indicate potential safety issues, strength of the association between drug and AE and is time saving. The higher the score, the stronger the statistical association. However, statistical associations may not necessarily always designate causal relationships and signals, albeit, indicate further investigation [53].

Signal Management Process

A safety signal is information regarding a new or known adverse event that may be caused by a medicinal product and requires further investigation. The European Medicines Agency (EMA), together with the regulatory authorities of the Member States and the marketing authorization holders (MAHs), are responsible for detecting and managing safety signals. These signals can be collected from a wide range of sources, such as spontaneous reports, clinical studies, and scientific literature. For example, the EudraVigilance database is

an important source of information regarding suspected adverse reactions and signals. The identification of a safety signal does not necessarily imply that a specific medicinal product caused the reported adverse event. The adverse event could also be due to other causes, such as concomitant diseases or other medications or substances taken by the patient. Therefore, the evaluation of safety signals serves to establish whether or not there is a causal relationship between the medicinal product and the reported adverse event. Therefore, it is part of routine pharmacovigilance activities and is essential to ensure that regulatory authorities have the most up-to-date information on the benefits and risks of a medicine. The signal management process is a set of activities performed to determine whether, based on a review of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, information in the scientific literature, or other data sources, there are new risks associated with an active substance or medicinal product, or whether known risks have changed, as well as to establish any related recommendations, decisions, and communications. The EU signal management process includes the following steps.

• **Signal detection:** The search for and/or identification of signals using data from any source**.**

• **Signal validation**: The phase of evaluating the data supporting the detected signal, to verify that the available documentation contains sufficient evidence to demonstrate the existence of a new potential causal association or a new aspect of a known association, thus justifying further, more in-depth analysis of the signal.

• **Signal confirmation**: The stage of the process in which it is decided whether or not a validated signal entered into the European Pharmacovigilance Issues Tracking Tool (EPITT) requires further analysis and prioritization by the PRAC (Pharmacovigilance Risk Assessment Committee). This should be done by the PRAC rapporteur or the (lead) Member State (MS) within 30 days of receiving the validated signal.

• **Signal analysis and prioritization**: The stage in which the PRAC determines whether a confirmed signal requires further evaluation and, if necessary, by what deadlines and within what procedural framework. This is based on an initial analysis of the signal's potential impact on patient health or public health and the benefit-risk balance of the medicinal product in question.

• **Signal assessment and recommendation for action:** The final step, led by the PRAC, evaluates all available data related to a signal to determine the need for regulatory intervention [54]

Reporting Process In Eudravigilance

Introduction

The EudraVigilance system is a centralized pharmacovigilance database developed and maintained by the European Medicines Agency (EMA). It is designed for the collection, management, and analysis of suspected adverse drug reactions (ADRs) related to medicinal products authorized in the European Economic Area (EEA). The reporting process within EudraVigilance is a structured and standardized mechanism that ensures timely detection of safety concerns and supports regulatory decision-making. This process follows internationally harmonized guidelines developed by the International Council for Harmonisation, particularly the ICH E2B (R3) standard for Individual Case Safety Reports (ICSRs).[55]

1. Identification of Adverse Drug Reactions

The first step in the reporting process is the identification of a suspected adverse drug reaction. An ADR is defined as any harmful or unintended response to a medicinal product occurring at normal therapeutic doses.

ADRs may be identified by:

- Healthcare professionals (physicians, pharmacists, nurses)
- Patients or caregivers

- Pharmaceutical companies
- Clinical trial investigators

The recognition of ADRs is essential for pharmacovigilance, as it provides the initial data required for safety monitoring. These reactions may vary from mild symptoms such as headache to serious outcomes like hospitalization or death.

2. Preparation of Individual Case Safety Reports (ICSRs)

Once an ADR is identified, it is documented in the form of an Individual Case Safety Report (ICSR). ICSRs are the fundamental units of data in EudraVigilance and provide comprehensive information about the patient and the adverse event.

Key Components of ICSRs

- Patient demographics (age, sex, medical history)
- Details of suspected medicinal product (dose, route, indication)
- Description of the adverse event (onset, duration, outcome)
- Concomitant medications
- Reporter information
- Causality assessment (if available)

The structure of ICSRs is standardized according to ICH E2B (R3) guidelines, ensuring consistency across different reporting systems.

3. Submission of Reports

3.1 Electronic Reporting

All ICSRs must be submitted electronically to EudraVigilance. Marketing Authorization Holders (MAHs) and National Competent Authorities (NCAs) use secure electronic gateways to transmit data.

Electronic reporting ensures:

- Faster communication
- Reduced transcription errors
- Standardized data formatting

3.2 Reporting Timelines

The reporting timelines are determined based on the seriousness of the ADR:

- **Serious ADRs**: Must be reported within 15 days
- **Non-serious ADRs**: Must be reported within 90 days

Timely reporting is crucial to ensure rapid detection of potential safety issues.

3.3 Direct Reporting by Patients and Healthcare Professionals

Patients and healthcare professionals can directly report ADRs to national regulatory authorities. These reports are then transmitted to EudraVigilance.

This approach enhances patient involvement and increases the volume of real-world safety data.

Data Validation And Quality Assurance In Eudravigilance

Introduction

The EudraVigilance system, maintained by the European Medicines Agency (EMA), plays a critical role in monitoring the safety of medicinal products across the European Economic Area (EEA). A key component of this system is **data validation and quality assurance**, which ensures that the information collected through Individual Case Safety Reports (ICSRs) is accurate, reliable, and suitable for signal detection and regulatory decision-making. Given that pharmacovigilance relies heavily on real-world data, maintaining high data quality is essential. Poor-quality data can lead to incorrect conclusions, delayed signal detection, and potential risks to public health.

1. Importance of Data Validation in Pharmacovigilance

Data validation is the process of verifying that submitted data meet predefined standards of completeness, accuracy, and consistency. In EudraVigilance, validation is essential because:

- It ensures regulatory compliance with international standards
- It enhances the credibility of safety data
- It supports accurate signal detection and analysis
- It minimizes errors such as duplication or incorrect classification[56]

Without proper validation, the large volume of ADR reports could become unreliable and difficult to interpret.

2. Levels of Data Validation in EudraVigilance

Data validation in EudraVigilance is conducted at multiple levels to ensure comprehensive quality assurance.

2.1 Technical Validation

Technical validation is the first step after submission of an ICSR. It focuses on verifying whether the report complies with the required electronic format defined by the International Council for Harmonisation E2B (R3) guidelines.

Key aspects include:

- Correct file structure and format
- Presence of mandatory fields
- Proper data encoding
- Valid transmission protocols

If a report fails technical validation, it is rejected and must be corrected before resubmission.

2.2 Business Validation

Business validation ensures that the content of the report meets regulatory and logical requirements.

This includes:

- Verification of report type (serious or non-serious)
- Consistency between different data fields
- Logical relationships (e.g., event date cannot precede drug administration)

Business rules help identify inconsistencies that may not be detected during technical validation.

2.3 Medical Validation

Medical validation involves the clinical assessment of the reported data.

Key elements include:

- Verification of adverse event descriptions
- Assessment of seriousness criteria
- Evaluation of causality (if provided)
- Review of patient history and concomitant medications

Medical validation ensures that the report is clinically meaningful and suitable for further analysis.

Coding And Standardization In Eudravigilance

Introduction

The EudraVigilance system, operated by the European Medicines Agency (EMA), is a central database for managing suspected adverse drug reaction (ADR) reports in the European Economic Area (EEA). One of the most critical aspects of this system is coding and standardization, which ensures that data collected from diverse sources are harmonized, comparable, and suitable for analysis.

Given the global nature of pharmacovigilance, ADR reports originate from different countries, languages, and healthcare systems. Without proper standardization, it would be extremely difficult to analyze this data effectively. Coding transforms raw clinical information into structured, standardized formats, enabling efficient data processing, signal detection, and regulatory decision-making.

1. Importance of Coding and Standardization

Coding and standardization are essential for:

- Ensuring consistency in data reporting
- Facilitating data comparison across regions and time periods
- Supporting automated data analysis and signal detection
- Enhancing data quality and reliability
- Enabling regulatory compliance with international guidelines

Without standardized coding systems, variations in terminology (e.g., “heart attack” vs. “myocardial infarction”) could lead to fragmented data and missed safety signals.

2. Role of Standard Terminologies

Standard terminologies are used to convert clinical descriptions into universally accepted codes. This ensures uniformity across all ICSRs submitted to EudraVigilance.

2.1 MedDRA (Medical Dictionary for Regulatory Activities)

The primary coding system used in EudraVigilance is MedDRA, developed under the International Council for Harmonisation.

Structure of MedDRA

MedDRA has a hierarchical structure consisting of five levels:

1. **System Organ Class (SOC)** – Broad classification (e.g., cardiac disorders)
2. **High-Level Group Terms (HLGT)**
3. **High-Level Terms (HLT)**

4. **Preferred Terms (PT)** – Standardized medical concept
5. **Lowest Level Terms (LLT)** – Synonyms or specific expressions

For example, different terms like "heart attack" or "cardiac infarction" are coded under the same Preferred Term: *myocardial infarction*.

Advantages of MedDRA

- Standardized medical terminology
- Multilingual support
- Hierarchical structure for detailed analysis
- Facilitates signal detection

2.2 Importance in Adverse Event Coding

All adverse events reported in ICSRs are coded using MedDRA terms. This allows:

- Grouping of similar cases
- Identification of trends
- Efficient statistical analysis

3. Drug Coding and Identification

In addition to adverse event coding, medicinal products must also be standardized.

3.1 Substance and Product Coding

Drugs are coded using standardized identifiers, including:

- Active substance names
- Brand names
- Pharmaceutical forms

This ensures that different reports referring to the same drug are correctly linked.

3.2 ISO IDMP Standards

EudraVigilance increasingly aligns with ISO Identification of Medicinal Products (IDMP) standards, which provide:

- Unique identifiers for medicinal products
- Standardized product information
- Improved traceability across regions

4. Coding Process in EudraVigilance

The coding process involves several steps:

4.1 Data Entry

Raw clinical data are collected from reporters, including descriptions of adverse events and drug information.

4.2 Term Selection

Trained coders select appropriate MedDRA terms that best represent the reported information.

4.3 Quality Check

Coding is reviewed to ensure:

- Accuracy of term selection
- Consistency with medical information
- Compliance with coding guidelines

4.4 Updating and Version Control

MedDRA is updated twice yearly. EudraVigilance ensures that:

- Coding is aligned with the latest version
- Historical data remain consistent

5. Challenges in Coding and Standardization

Despite its advantages, coding presents several challenges:

5.1 Ambiguity in Reporting

Reports may contain vague or incomplete descriptions, making accurate coding difficult.

5.2 Human Error

Manual coding can lead to inconsistencies or incorrect term selection.

5.3 Language Differences

Reports from different countries may require translation before coding.

5.4 Complexity of Medical Terminology

Some clinical conditions may not have straightforward equivalents in MedDRA.

6. Quality Assurance in Coding

To address these challenges, EudraVigilance implements strict quality control measures:

- Training programs for coders
- Standard operating procedures (SOPs)
- Automated coding tools
- Regular audits and reviews

These measures ensure high levels of accuracy and consistency.

7. Role of Automation and Technology

Technological advancements are improving coding efficiency:

7.1 Auto-Coding Systems

Software tools can automatically suggest MedDRA terms based on text inputs.

7.2 Natural Language Processing (NLP)

NLP techniques analyze free-text data and convert them into structured codes.

7.3 Artificial Intelligence (AI)

AI systems enhance accuracy by learning from previous coding decisions.[57]

Role Of Stakeholders In Eudravigilance

1. European Medicines Agency (EMA)

The EMA is the central authority responsible for managing EudraVigilance and coordinating pharmacovigilance activities across the European Union.

Key Responsibilities

- Maintenance and development of the EudraVigilance database
- Monitoring and analysis of ADR data
- Coordination of signal detection activities
- Ensuring compliance with regulatory requirements
- Providing access to safety data for stakeholders

The EMA also supports the **Pharmacovigilance Risk Assessment Committee (PRAC)**, which evaluates safety signals and recommends regulatory actions[58].

2. National Competent Authorities (NCAs)

National Competent Authorities are regulatory bodies within individual EU member states responsible for pharmacovigilance at the national level.

Roles of NCAs

- Collection of ADR reports from healthcare professionals and patients
- Submission of reports to EudraVigilance
- Monitoring of drug safety within their jurisdiction
- Implementation of regulatory decisions at the national level

NCAs act as a bridge between local healthcare systems and the centralized EudraVigilance database, ensuring comprehensive data collection.

3. Marketing Authorization Holders (MAHs)

Marketing Authorization Holders (pharmaceutical companies) are legally responsible for the safety of their medicinal products.

Key Responsibilities

- Collection and reporting of ADRs related to their products
- Submission of ICSRs to EudraVigilance within specified timelines
- Continuous monitoring of product safety
- Conducting post-authorization safety studies (PASS)
- Preparing periodic safety reports such as PSURs

MAHs play a proactive role in pharmacovigilance by ensuring that safety data are continuously evaluated and reported.

4. Healthcare Professionals

Healthcare professionals, including doctors, pharmacists, and nurses, are among the primary sources of ADR reporting.

Roles and Contributions

- Identification and reporting of suspected ADRs

- Providing detailed clinical information
- Supporting causality assessment
- Participating in pharmacovigilance awareness programs

Their clinical expertise ensures that reports are accurate and medically meaningful, which is critical for signal detection.

5. Patients and Consumers

Patients and consumers are increasingly recognized as important contributors to pharmacovigilance systems.

Importance of Patient Reporting

- Provides real-world experience of drug use
- Highlights quality-of-life issues
- Identifies ADRs that may not be reported by healthcare professionals

Patient reports may lack clinical detail but offer valuable insights into the impact of medicines in everyday settings.

6. Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC is a scientific committee within the EMA responsible for assessing and monitoring the safety of human medicines.

Functions of PRAC

- Evaluation of safety signals
- Assessment of risk-benefit balance
- Recommendation of regulatory actions
- Review of risk management plans

PRAC plays a critical role in translating data from EudraVigilance into actionable regulatory decisions.

7. International Organizations

Global organizations contribute to pharmacovigilance by promoting international collaboration and standardization.

Key Organizations

- World Health Organization (WHO)
- International Council for Harmonisation

Roles

- Development of global pharmacovigilance guidelines
- Harmonization of reporting standards
- Facilitation of data sharing across countries

These organizations ensure that EudraVigilance aligns with global pharmacovigilance practices.

8. Academic and Research Institutions

Universities and research organizations contribute to pharmacovigilance through:

- Data analysis and interpretation
- Methodological research in signal detection

- Training and education programs

Their work enhances the scientific basis of pharmacovigilance activities.

9. Collaboration Among Stakeholders

The success of EudraVigilance depends on effective collaboration among stakeholders.

Key Aspects of Collaboration

- Timely sharing of safety data
- Standardization of reporting practices
- Joint evaluation of safety signals
- Coordinated regulatory actions

Limitations Of Eudravigilance

1. Underreporting of Adverse Drug Reactions

One of the most significant limitations of EudraVigilance is underreporting of adverse drug reactions (ADRs**)**. Not all adverse events experienced by patients are reported to the system.[59]

Causes of Underreporting

- Lack of awareness among healthcare professionals
- Time constraints in clinical practice
- Perception that only serious ADRs need reporting
- Limited patient awareness of reporting systems

Impact

Underreporting leads to incomplete datasets, making it difficult to detect rare or long-term adverse effects. It can delay signal detection and reduce the sensitivity of the pharmacovigilance system.

2. Variable Data Quality

The quality of data in EudraVigilance can vary significantly across reports.

Common Data Quality Issues

- Missing or incomplete information
- Inaccurate patient details
- Lack of follow-up data
- Poor documentation of clinical outcomes

Impact on Signal Detection

Low-quality data can lead to:

- Misinterpretation of safety signals
- Reduced reliability of statistical analyses
- Difficulty in establishing causality

3. Reporting Bias

EudraVigilance data are subject to various forms of reporting bias.

Types of Reporting Bias

- **Stimulated reporting**: Increased reporting following media coverage or regulatory alerts

- **Selective reporting**: Tendency to report severe or unusual ADRs more frequently
- **Geographical bias**: Differences in reporting practices across countries

Consequences

Reporting bias can distort the true incidence of adverse events and lead to overestimation or underestimation of risks.

4. Difficulty in Establishing Causality

One of the major challenges in pharmacovigilance is determining whether a drug actually caused an adverse event.

Reasons

- Presence of multiple concomitant medications
- Underlying diseases
- Lack of detailed clinical information
- Absence of controlled study conditions

Impact

EudraVigilance primarily captures suspected associations, not confirmed causal relationships. This limits the ability to draw definitive conclusions about drug safety.

5. Duplicate Reporting

Duplicate reports occur when the same adverse event is reported multiple times by different sources.

Sources of Duplication

- Reports from both healthcare professionals and pharmaceutical companies
- Multiple submissions from different countries
- Follow-up reports incorrectly classified

Impact

- Inflation of case counts
- Distortion of statistical analyses
- Increased workload for data management

Although EudraVigilance uses algorithms to detect duplicates, complete elimination remains challenging.

6. Lack of Denominator Data

EudraVigilance lacks accurate data on the total number of patients exposed to a particular drug.

Implications

- Inability to calculate incidence rates
- Difficulty in comparing risks between drugs
- Limited quantitative risk assessment

Without denominator data, signal detection relies heavily on disproportionality analysis rather than true risk estimation.

7. Limitations of Statistical Methods

Signal detection in EudraVigilance relies on statistical techniques such as disproportionality analysis.

Challenges

- False positives (identifying signals that are not real)
- False negatives (missing true safety signals)
- Sensitivity to data quality and reporting patterns

Impact

Statistical methods can identify associations but cannot confirm causality, requiring further clinical evaluation.

8. Delayed Reporting

Timeliness is crucial in pharmacovigilance, but delays in reporting can occur.

Reasons for Delays

- Administrative processes
- Lack of awareness
- Delayed recognition of ADRs
- Inefficient reporting systems

Consequences

Delayed reporting can postpone signal detection and regulatory action, potentially increasing patient risk.

9. Complexity of the System

EudraVigilance is a highly complex system with detailed reporting requirements.

Challenges

- Technical difficulties in electronic submission
- Need for specialized training
- Compliance with multiple regulatory guidelines

Impact

Complexity may discourage reporting, especially among smaller healthcare institutions or less experienced users.

10. Variability Across Countries

Differences in healthcare systems, regulatory practices, and reporting cultures across EU member states can affect data consistency.

Examples

- Variation in reporting rates
- Differences in data quality
- Inconsistent application of guidelines

Impact

This variability complicates data analysis and may affect the comparability of results.

11. Limited Clinical Detail in Reports

Many ICSRs lack detailed clinical information necessary for thorough evaluation.

Missing Information

- Laboratory results
- Imaging findings
- Detailed patient history
- Information on rechallenge or dechallenge

Impact

Insufficient clinical detail limits the ability to assess the severity and causality of ADRs.

12. Challenges in Signal Validation

Even when a potential signal is detected, validating it can be difficult.

Reasons

- Lack of supporting evidence
- Confounding factors
- Limited number of cases[60]

Impact

Signal validation often requires additional studies, which can be time-consuming and resource-intensive.

Conclusion

The EudraVigilance system represents a cornerstone of modern pharmacovigilance within the European Union, enabling the systematic collection, management, and analysis of suspected adverse drug reactions (ADRs). Managed by the European Medicines Agency (EMA), it provides a robust and standardized platform for monitoring the safety of medicinal products throughout their lifecycle.

The reporting process in EudraVigilance, based on Individual Case Safety Reports (ICSRs), ensures that safety data from healthcare professionals, patients, and pharmaceutical companies are captured in a structured and harmonized manner. The use of internationally accepted standards developed by the International Council for Harmonisation enhances data consistency, quality, and global compatibility. Furthermore, rigorous validation, coding (such as MedDRA), and quality assurance processes contribute to the reliability of the database.

Signal detection is a key strength of the system, combining statistical methods with clinical evaluation to identify new or emerging safety concerns. The structured signal management process—comprising detection, validation, prioritization, and regulatory action—ensures that potential risks are assessed efficiently and addressed appropriately. Regulatory bodies such as the Pharmacovigilance Risk Assessment Committee (PRAC) play a vital role in translating these findings into public health actions.

Despite its effectiveness, the system faces limitations such as underreporting, variability in data quality, reporting bias, and challenges in establishing causality. However, ongoing advancements in technology, including automation and artificial intelligence, along with improved stakeholder engagement, are continuously strengthening the system.

In conclusion, EudraVigilance is an essential tool for safeguarding public health by enabling early detection of drug-related risks and supporting evidence-based regulatory decisions. Its continued development and optimization will further enhance global pharmacovigilance efforts and ensure the safe use of medicines.

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