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REVIEW OF PHARMACOVIGILANCE

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ABSTRACT

Medicines and vaccines have transformed the prevention and treatment of diseases. In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and / or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem. All medicines and vaccines undergo rigorous testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for ashort period of time. Certain side effects may only emerge once these products have been used by a heterogenous population, including people with other concurrent diseases, and over a long period of timetime. Pharmacovigilance (PV, or PhV), also known as drug safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.

KEYWORDS: Pharmacovigilance, Adverse effects, WHO, Adverse drug reaction, Adverse events, Toxic effects and Synergic.

INTRODUCTION

The World Health Organization defines pharmacovigilance (PV) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. The goals of PV are to bolster patient safety concerning medicine use by providing a system to collect, assess, and distribute drug safety data. PV activities involve monitoring approved drugs and investigational medicinal products (IMPs) to: Identify previously unknown adverse effectsRecognize changes in the frequency or severity of known adverse effectsAssess a drugs risk/benefit to determine if action is required to improve safety Ensure the accuracy of information communicated healthcare professionals and patients, and to ensure information contained in patient information leaflets (PILs) is up to date.

Pharmacovigilance Service
*Pharmacovigilance consulting
*Pharmacovigilance outsourcing
*support services outsourcing
*specialist support outsourcing
*Pharmacovigilance operation clinical trial

Life Cycle of Pharmacovigilance Services

Uniquely placed to provide all your pharmacovigilance requirements to assist your Company in the implementation of any Corrective or Preventative Actions (CAPA) necessary, using 'RISK' based methodology regardless of where your product at during its life cycle for pharmacovigilance activities. As specialist Pharmacovigilance service provider, PrimeVigilance can also provide experienced auditors for your global auditing requirements.

PrimeVigilance is an industry leader in providing QPPV services and is equipped with fully supported safety database solutions for a compliant and effective pharmacovigilance system together with innovative technologies, which include Intelligent Automation.

Pharmacovigilance Outsourcing

Pharmacovigilance outsourcing company should enable its clients to interact with one service provider for all the Pharmacovigilance (PV) and regulatory requirements, which translates into a cost and time effective strategy.

Pharmacovigilance outsourcing to PrimeVigilance is not geographically restricted only to EEA countries. On the contrary, we have been successfully handling clients from all over the world. In brief, we have many of our clients located in Europe, US, Australia, the Middle East and Asia and as a result of their products distribution, marketing authorisation status and study sites we are responsible for clinical and/or post-marketing PV services for approximately over 4,500 medicinal products distributed across more than 100 countries globally.

For over a decade now, PrimeVigilance stands out among pharmacovigilance service providers worldwide. Pharmacovigilance consulting services offered by PrimeVigilance consist of but are not limited to consulting services – e.g. benefit-risk analysis, Safety data exchange agreement (SDEA) development, and development of standard operating procedures (SOPs), European Economic Area (EEA) Qualified Persons for Pharmacovigilance (QPPV), local QPPVs, Auditing services, aggregate report writing, clinical trial and post-marketing case processing, safety database, data migration, regulatory reporting, development of risk management plans (RMPs), Signalling (detection, evaluation and validation), literature search, development of the pharmacovigilance system master file (PSMF), publishing and submission.

What is pharmacovigilance in clinical researchers

Pharmacovigilance begins with clinical trials that provide data on the benefits and risks of a drug. The aim of pharmacovigilance in clinical research is to determine if the benefits outweigh the risks; if they do, drug manufacturers take steps to gain approval to market the new drug.Phase I, II, and III clinical trials are needed before a drug company can apply for a new medicine's market authorization. In these studies, the principle investigator is the main point of contact at the trial site. They are responsible for the conduct of the research and then feed it back to the sponsor (the pharma company).During clinical trials, the investigator collects and analyzes data on serious adverse events (SAEs), determining whether the drug in question caused the SAEs. If they conclude that the negative side effects were causal, they are categorized as adverse drug reactions (ADRs).The investigator shares this data with the pharmaceutical company responsible for the drug's R&D (research and development). This is assessed by the pharmaceutical company's in-house PV team and the patient files undergo medical review. The PV team

determines if the drug is sufficiently safe and effective to progress to the next phase of clinical research or to submit an application to the regulatory authority for approval to go to market.These regulatory authorities have the final word as to whether the drug's safety and efficacy profile is acceptable.If approved, Phase IV clinical trials may be conducted by the drug company to provide additional data on the safety profile and efficacy of a drug. These studies are beneficial as they provide data in a less controlled environment, representative of how patients are using the drug.

Members of country there in WHO program for International drug monitoring

WHO Programme for International Drug Monitoring.A vital, global collaboration to protect patients from the harm that medicines can cause.

What is the WHO programme

The WHO Programme for International Drug Monitoring is a group of more than 150 countries that share the vision of safer and more effective use of medicines. They work nationally and collaborate internationally to monitor and identify the harm caused by medicines, to reduce the risks to patients and to establish worldwide pharmacovigilance standards and systems. UMC has been responsible for the technical and operational aspects of the programme since 1978.The WHO programme was created in 1968 to ensure that evidence about harm to patients was collected from as many sources as possible. This would enable individual countries to be alerted to patterns of harm that were emerging across the world and which might not be evident from their local data alone.

Members of the WHO programme

Currently 149 countries are members of the WHO Programme for International Drug Monitoring. Another 23 associate members are in the early stages of establishing their pharmacovigilance systems in preparation for full membership.

In 1968, during the 16th World Assembly the 16.36 resolution called for "a systematic collection of information on serious adverse drug reactions during the development and particularly after medicines have been made available for public use". This led to the formation of the WHO Programme for International Drug Monitoring (PIDM).WHO promotes PV at country level. Initially the WHO PIDM members consisted of 10 countries. As of October 2021, 149 members have joined the WHO PIDM, and in addition 23 associate members are awaiting full membership. WHO PIDM Members submit reports of adverse reactions associated with medicinal products, known as Individual Case Safety Reports (ICSRs) to the WHO global database, VigiBase. VigiBase is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, known as Uppsala Monitoring Centre. In October 2021, there were over 28 million reports of adverse reactions in VigiBase. Data in VigiBase are recorded in a structured and comprehensive way to allow the detection of potential medicinal safety hazards.In April 2015, WHO launched VigiAccess. VigiAccess is a new web application that will allow anyone to access information and encourage the reporting of adverse effects from medicinal products.

Pharmacovigilance program of India

The Pharmacovigilance Programme of India (PvPI) is an Indian government organization which identifies and responds to drug safety problems. Its activities include receiving reports of adverse drug events and taking necessary action to remedy problems. The Central Drugs Standard Control Organisation established the program in July 2010 with All India Institute of Medical Sciences, New Delhi as the National Coordination Centre, which later shifted to Indian Pharmacopoeia Commission in Ghaziabad on 15 April 2011.Many developed countries set up their pharmacovigilance programs following the Thalidomide scandal in the 1960s. India set up its program in the 1980s. This general concept of drug safety monitoring went through different forms, but the Central Drugs Standard Control Organisation established the present Pharmacovigilance Program of India in 2010.Now the program is well integrated with government legislation, a regulator as leader, and a research center as part of the Indian Pharmacopoeia Commission. As of 2018 there were 250 centers around India capable of responding to reports of serious adverse reactions. One of the challenges of the organization is training doctors and hospitals to report adverse drug reactions when patients have them. The Pharmacovigilance Program makes these reports itself, but ideally, such reports could originaten from any clinic.The Pharmacovigilance Programme seeks to encourage a culture and social expectation of reporting drug problems. One of the successes of the program was detecting adverse effects of people in India using carbamazepine. While this drug is safer among people native to the Europe, people of South Asia have different genetics and are more likely to experience problems when using it. Other countries could not have been able to detect this problem, and the Pharmacovigilance Programme's detection of it was a success story.The establishment of the Pharmacovigilance Program made India a more attractive international destination for foreign companies to bring clinical trials research. Understanding the quality of India's pharmacovigilance programme is key to international researchers conducting trials in India.The program collaborates both in India and internationally with the World Health Organization on projects for safe medication. As a collaborating center, the Pharmacovigilance Programme assists the WHO in developing international policy for other countries to manage their own drug safety programs.While the United States and Europe have pharmacovigilance systems which are developed well in some ways, the Indian programme has more and specialized expertise to apply for the unique circumstances of India. The Pharmaceutical industry in India produces more drugs

than any other national industry. Because of the large amount of drugs and the many countries which import them, the Indian program monitors in some ways more than anywhere else.

How many regional pharmacovigilance Centres are there in India

5 regional pharmacovigilance centers

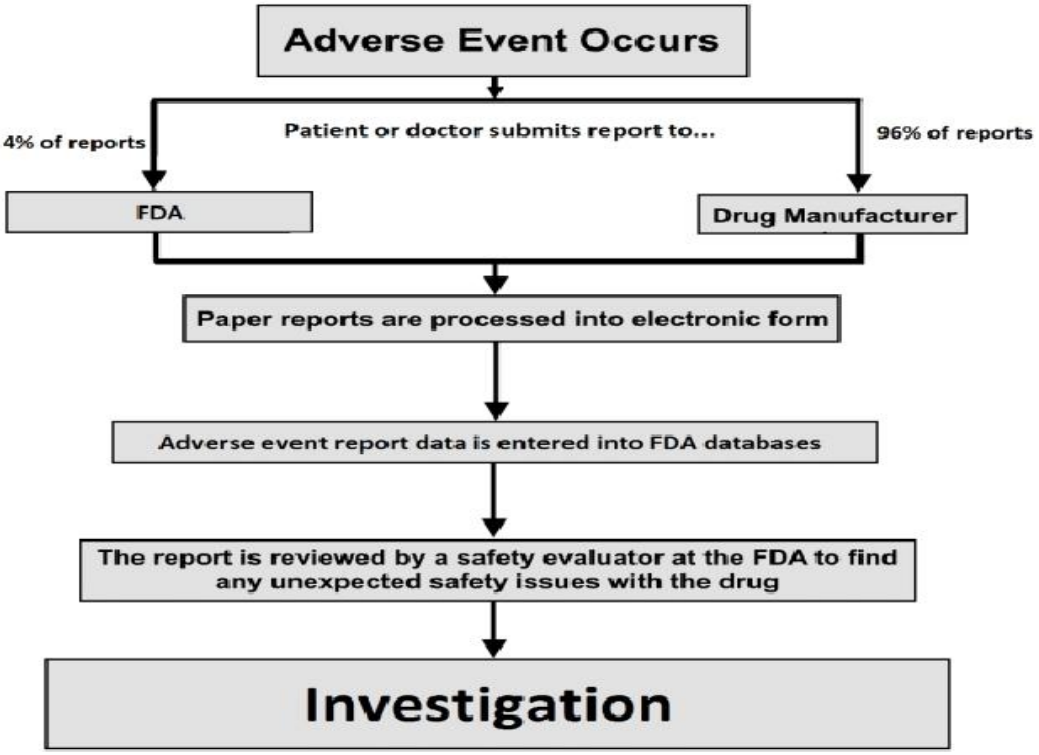
There are 5 regional pharmacovigilance centers located at Kolkata (IPGMR-SSKM Hospitals), Mumbai (TN Medical College & BYL Nair Charitable Hospital), Nagpur (Indira Gandhi Medical College), New Delhi (Lady Hardinge Medical College) and Pondicherry (JIPMER)

What's Adverse Events

ADVERSE EVENTS

Definitions

• Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. [From ICH E2A and E6, "investigational" term only in E6].An adverse event is any untoward or unfavorable medical occurrence in a human Subject, including any abnormal sign (for example, abnormal physical exam ornbla boratory finding), symptom, or disease, temporally associated with the subiparticipation in the research, whether or not considered related to the subject'sparticipation in the research. Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.



Categories of Adverse Events

• Adverse Drug Reactions

In the pre-approval clinical experience with a new medicinal product or its new. usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). [From ICH E6]

• Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the

ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

• Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

• Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

• Treatment Emergent Adverse Event

An AE for which the start date is on or after the date that the intervention began.

• Serious Adverse Events.

SAEs are a subset of adverse events.

An SAE is defined as any untoward medical occurrence that meets any of the following criteria:

▪ results in death

▪ is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. [Explanatory text from ICH E2A])

▪ requires inpatient hospitalization or prolongation of existing hospitalization

▪ results in persistent or significant disability/incapacity is a congenital anomaly/birth defect [Bullets 1-5 from ICH E2A and E6] In addition, an important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [Adapted from OHRP Guidance]

{Some protocols may list events specific to the protocol that should be reported as serious. Examples might be post-extraction bleeding in anticoagulated participants and anaphylactic reaction after lidocaine or analgesic administration.} An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal functions, or a congenital anomaly/birth defect. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse Drug Reactions

An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.1 Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorised use of a medicinal product in normal doses.2 While this change potentially alters the reporting and surveillance carried out by manufactures and medicines regulators, in clinical practice it should not affect our approach to managing ADRs.

Seminal research undertaken in the late 20th and early 21st century in the USA and the UK demonstrated that ADRs are a common manifestation in clinical practice, including as a cause of unscheduled hospital admissions, occurring during hospital admission and manifesting after discharge.3–6 The incidence of ADRs has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts. Inevitably, the event frequency is associated with the method used to identify such events and the majority of ADRs do not cause serious systemic manifestations. Nevertheless, this frequency of potential harm needs to be considered carefully because it has associated morbidity and mortality, can be financially costly and has a potentially negative effect on the prescriber-patient relationship.

Medicines that have been particularly implicated in ADR-related hospital admissions include antiplatelets, anticoagulants, cytotoxics, immunosuppressants, diuretics, antidiabetics and antibiotics. Fatal ADRs, when they occur, are often attributable to haemorrhage, the most common suspected cause being an antithrombotic/anticoagulant co-administered with a non-steroidal anti-inflammatory drug (NSAID).[7]

Classification of adverse drug reactions

Traditionally, ADRs have been classified into two types.

•Type A reactions – sometimes referred to as augmented reactions – which are 'dose-dependent' and predictable on the basis of the pharmacology of the drug.

•Type B reactions – bizarre reactions – which are idiosyncratic and not predictable on the basis of the pharmacology.

Preventing adverse drug reactions.

While some ADRs are unpredictable – such as anaphylaxis in a patient after one previous uneventful exposure to a penicillin-containing antibiotic – many are preventable with adequate foresight and monitoring. Preventability (or avoidability) usually refers to when the drug treatment plan is inconsistent with current evidence-based practice or is unrealistic when taking known circumstances into account.10 Epidemiological studies tend to find that between a third and a half of ADRs are (at least potentially) preventable although preventability is much easier to diagnose in hindsight. However, interventions that reduce the probability of an ADR occurring can be an important way to reduce the risk of patient harm.

There are two basic steps that can be followed to prevent an ADR occurring.

Identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment choice accordingly.

Ensure the treatment plan mitigates any possible adverse effects.

Diagnosing adverse drug reactions

ADRs are one of the great mimics in healthcare, often emulating 'traditional diseases' and manifesting in all systems of the body. Drug-related problems in patients admitted to hospital may present in many different ways, including weakness or drowsiness, biochemical or haematological derangements (such as acute kidney injury, electrolyte imbalance or anaemia), bleeding, gastrointestinal disturbances, hypoglycaemia or healthcare-associated infections such as Clostridium difficile. However, rarer manifestations – such as drug-induced lupus, fixed drug eruptions, drug-induced eosinophilia or angioedema – require a level of vigilance and suspicion on behalf of the clinician who should look very hard to identify a causative agent. A comprehensive medication history is fundamental in identifying any possible connection between a presenting complaint or subsequent finding and an ADR, as well as preventing future ADRs. Various criteria can help in attributing causality to a particular drug.

Managing adverse drug reactions

Altering a dosage regimen or withdrawing a medicine suspected of causing an ADR are common methods of managing ADRs in practice. However, the course taken to manage an ADR is likely to vary from clinician to clinician. Under EU legislation, the approval of all new medicines onto the market must now be accompanied by a robust risk management plan from the marketing authorisation holder, which may involve the development of specific treatments for managing specific ADRs, as well as ongoing safety trials. Such has been the case with antidotes for direct oral anticoagulant-induced bleeding.

•A summary table showing primary ADR detection approaches and evaluation methodologiesmethodologies.

Study	Research aim	Primary approach(es)	Evaluation methodology
Leaman et al.	Concept/relation extraction	Lexicon-based (450 comments for system development)	Quantitative. Against manually annotated data (3150 instances)
Nikfarjam and Gonzalez	Concept/relation extraction	Lexical pattern-matching (2400 comments for pattern building). Association rule mining to identify patterns	Quantitative. Against manually annotated data (1200 instances)
Chee et al.	Drug classification	Ensemble classification using drug categories as classes	Mixed. Classification results are combined to generate drug scores for 3 drugs, which are compared against scores for drugs (12) with known adverse effects
Benton et al.	Concept/relation extraction	Lexicon-based. Association rule mining to identify drug-reaction pairs	Quantitative. Adverse reactions associated with drugs obtained from product labels and compared against system reported adverse events
Hadzi-Puric and Grmusa	Concept/relation extraction	Lexicon-based approach for ADR detection. Statistical scoring for identifying drug-relation	Mixed. Qualitative analysis of identified ADRs against known ADRs. Recall, precision and F-score

		associations	computed for evaluation against annotated data
Yang et al.	Concept/relation extraction	Lexicon-based. Association rule mining to identify drug-reaction pairs	Quantitative. FDA AERS used as the gold standard. Lift, Leverage, and Proportional Reporting Ratio used as metrics
Bian et al.	ADR classification	Classification of tweets using Support Vector Machine (SVM) classifiers. Two classifiers built: one to predict if a user has used a drug (based on the tweets), and the second to classify if a post contains an adverse effect	Mixed. Evaluation and training is performed on the same data. Only classification accuracies reported. Analysis describes the limitations introduced by noise in Twitter
Liu and Chen	Concept/relation extraction	Lexicon-based approach for ADR and drug detection. Shortest dependency path based machine learning algorithm for relation extraction	Quantitative. Separate evaluations for entity extraction, ADR detection and classification of patient experiences using 200 manually annotated comments
Yang et al.	ADR classification	A combination of supervised and unsupervised approaches for training binary classifiers. A mixture of syntactic, semantic, and sentiment features are used to train SVM and Naïve Bayes classifiers	Quantitative. Evaluation performed on 1600 annotated instances. Evaluation demonstrates that the combination of supervised and unsupervised training performs significantly better than using supervised training only
Jiang and Zheng	Concept/relation extraction and classification	Supervised classification of tweets using a Maximum Entropy classifier trained on a data set of 600 tweets only. MetaMap to identify drug and ADR categories	Mixed. 285 tweets for testing the classification accuracy. ADR extraction accuracy is evaluated against known adverse reactions
Yates and Goharian	Concept/relation extraction	Pattern-based. 7 patterns used for extracting ADRs from approximately 125 manually annotated comments	Quantitative. Against manually annotated data (125 instances)
Yeleswarapu et al.	Concept/relation extraction	Lexicon-based. Prepared lexicon used for drug and ADR detection. Association rule mining and BCPNN used for identifying drug-symptom and drug-disease pairs	Qualitative. Evaluation is performed via comparative analysis with findings from previous studies. Primary conclusion of evaluation is that combining social media data with other sources such as medical literature and ADR databases can improve ADR detection performance
Freifeld et al.	Concept/relation extraction	Lexicon-based. A prepared lexicon is used to detect ADRs. Aggregated frequencies are used to compare drug-reaction pairs	Quantitative. Aggregated frequency of identified product-event pairs compared with data from AERS. Correlation between the two sources computed to assess the effectiveness of social media as a resource for ADR monitoring
Segura-Bedmar et al.	Concept/relation extraction	Lexicon-based. A prepared lexicon was used in a multi-lingual text analysis engine to detect drugs and ADRs in text	Quantitative. Against manually annotated data (400 instances). Drug and ADR detection evaluated separately
Ginn et al.	Corpus presentation/description. Supervised learning experiments to illustrate utility of corpus	Supervised classification of ADR assertive tweets using 10-fold cross validation over a large annotated data set of 10,822 tweets. Data set artificially balanced to lower ADR-noADR	Quantitative. Evaluated against annotated data on the artificially balanced data set

		class imbalance	
Liu et al.	Medical entity extraction, adverse event extraction, report source classification	Lexicon-based approach for entity extraction and ADR extraction. Rule-based approach for relation classification	Quantitative. Against manually annotated data (600). Same set of instances used for the tasks of events and treatments recognition, ADR identification, and patient report extraction
Patki et al.	ADR/drug classification	Supervised classification of ADR assertive comments using SVMs and a rich set of features extracted via NLP techniques. Probabilities of all comments associated with each drug combined to predict if drug should be categorized as normal or blackbox	Mixed. Annotated data used for evaluating the classification task. Accuracy values used for evaluating drug categorization strategy
O'Connor et al.	Concept/relation extraction	Lexicon-based approach for detecting ADR mentions in Twitter data. Lexicon created by combining several existing ADR lexicons	Quantitative. Against manually annotated data (1873 instances)
Yang et al.	Drug-ADR relation extraction	Lexicon-based approach for detecting ADR mentions. Association rule mining to identify relationships between drugs and ADRs	Quantitative. Lift and Proportional Reporting Ratio for scoring association of ADRs with drugs. Recall, precision and F-measure used to compare the performance against three publicly available systems[a]
Sampathkumar et al.	Concept/relation extraction and relationship (causal) identification	Lexicon-based approach for detecting mentions of ADRs. Hidden Markov Model applied to detect relationship between drug-ADR pairs	Mixed. 10-fold cross validation against manually annotated data (2000 instances). Extracted ADRs compared against drug package labels to verify performance and to identify unknown ADRs
Sarker and Gonzalez	ADR classification	Supervised classification to detect ADR assertive texts. Features incorporated from distinct research areas such as sentiment analysis, polarity classification and topic modeling. Multiple corpora combined to boost classification performance	Quantitative. F-score for the ADR class is computed against gold standard annotations

•Individual Case Safety Reports (ICSR) in Pharmacovigilance.

I .C. S. R

The WHO Programme (World Health Organization) is a specialized agency of the United Nations. The goal of this organization is to "achieve better health for all through prevention and control of diseases." One way they do this is by tracking adverse events that happen during medical procedures, including pharmacovigilance. Pharmacovigilance is an important part of any healthcare system due to its ability to protect patients from harm or death caused by drugs, vaccines, and other products used in healthcare settings. ICSRs are a type of report that can be submitted on behalf of an individual patient as opposed to a group; these reports are stored in VigiBase which was created by the UMC (United Medical Consortium).

What does ICSR stand for

The individual case study report

ISO ICSR aims at establishing the same format for the reports on individual cases of suspected side effects in patients due to a medicine across the world. It also is expected to include better information on medicines that might be associated with an adverse drug reaction and on the therapeutic uses of those medicines. In addition, the standard also strengthens personal data protection in the records of ICSRs collected by pharmaceutical companies and regulatory authorities.This will improve the quality of data collected, and increase the ability to search and analyse them. Regulatory authorities will be able to detect and address safety issues with medicines more quickly, and therefore better protect patients.

•The Importance of Individual Case Study Reports (ICSR) to PharmacovigilancePharmacovigilance.

ICSRs are important because they provide a different perspective than adverse event reports, which can be collected from multiple patients. ICSR is an individual case safety report that includes data on individuals who have had experience with the medical treatments or products we want to know about. These types of cases may not always represent the same information as other studies.

Adverse event reporting

The individual case study report (ICSR) is an adverse event report for an individual patient and is the source of data in pharmacovigilance. The main focus of ICSRs are reports from healthcare providers and patients in member countries of the WHO Programme. A WHO global individual case safety report database (VigiBase) is maintained and developed on behalf of the WHO by the UMC.One of the fundamental principles of adverse event reporting is the determination of what constitutes an Individual Case Safety Report (ICSR). During the triage phase of a potential adverse event report, it is important to determine if the "four elements" of a valid ICSR are present:

•an identifiable patient
•an identifiable reporter (called the "verbatim")
•a suspect drug
•an adverse event

ICSR in pharmacovigilance

The ICSR (Individual Case Study Report) is the source of data in pharmacovigilance. WHO developed a global individual case safety report database, VigiBase, and it is maintained by UMC on behalf of WHO. In this article we will discuss what an ICSR is and why they are important to the process. One purpose that pharmacovigilance provides to the public is to help understand any possible risk associated with medicines or medical devices that have been approved for use and how they should be used safely and effectively. An ICSR (Individual Case Study Report) is the source of data in pharmaco vigilance process – it helps provide understanding about risks related to drugs/medical devices approved for usage.

VigiBase

VigiBase is the single largest drug safety data repository in the world. Since 1978, the Uppsala Monitoring Centre (UMC; established in Uppsala, Sweden) on behalf of WHO, have been maintaining VigiBase. Vigibase is used to obtain the information about a safety profile of a medicinal product. These data are used by pharmaceutical industries, academic institutions and regulatory authorities for statistical signal detection, updating periodic reports, ICSR comparisons with company databases and studying the reporting patterns. The data is collected from each of its 110 member states. About a hundred thousand ICSRs are added each year.

Seriousness determination

Although somewhat intuitive, there are a set of criteria within pharmacovigilance that are used to distinguish a serious adverse event from a non-serious one. An adverse event is considered serious if it meets one or more of the following criteria:

•results in death, or is life-threatening
•requires inpatient hospitalization or prolongation of existing hospitalization
•results in persistent or significant disability or incapacity
•results in a congenital anomaly (birth defect)
•or is otherwise "medically significant" (i.e., that it does not meet preceding criteria, but is considered serious because treatment/intervention would be required to prevent one of the preceding criteria.)

ISO ICSR standard

Coding of adverse events

Adverse event coding is the process by which information from an adverse effect reporter, is coded using standardized terminology from a medical coding dictionary, such as MedDRA (the most commonly used medical coding dictionary). The purpose of medical coding is to convert adverse event information into terminology that can be readily identified and analyzed. For instance, Patient 1 may report that they had experienced "a very bad headache that felt like their head was being hit by a hammer" [Verbatim 1] when taking Drug X. Or, Patient 2 may report that they had experienced a "slight, throbbing headache that occurred daily at about two in the afternoon" [Verbatim 2] while taking Drug Y. Neither Verbatim 1 nor Verbatim 2 will exactly match a code in the MedDRA coding dictionary. However, both quotes describe different manifestations of a headache. As a result, in this example both quotes would be coded as PT Headache (PT = Preferred Term in MedDRA).

Causality or Relatedness Assessment in Adverse Drug Reaction

Causality assessment essentially means finding a causal association or relationship between a drug and drug reaction. Identifying the culprit drug or drugs can be lifesaving or helpful in preventing the further damage caused by the drug to our body systems. In dermatology practice, when it comes to cutaneous adverse drug reaction, this is much more important and relevant because many aetiologies can produce a similar cutaneous manifestation. There are multiple criteria or algorithms available as of now for establishing a causal relationship in cases of adverse drug reaction (ADR), indicating that none of them is specific or complete. Most of these causality assessment tools (CATs) use four cardinal principles of diagnosis of ADR such as temporal relationship of drug with the drug reaction, biological plausibility of the drug causing a reaction, dechallenge, and rechallenge. The present study reviews some of the established or commonly used CATs and its implications or relevance to dermatology in clinical practice.

Causality assessment essentially means finding a causal association or relationship between a drug and a drug reaction. It is an evaluation of the likelihood that a particular treatment is the cause of an observed adverse event (AE).[1] This is an important and challenging part of pharmacovigilance, in which attempts are made to find out the exact drug responsible for causing drug reaction. This is important in clinical practice as more and more drugs are flooding the market and are used by our patients and more likely to cause side effects besides its effects. In the pursuit of efficacy, safety of these drugs is usually ignored. As the safety of the patients is more important than efficacy, identifying the culprit drugs becomes much more essential. The principles and methods of causality assessment or causality assessment tool (CAT) help clinicians to identify the culprit drugs. There are multiple criteria or algorithms available as of now for establishing a causal relationship in cases of adverse drug reaction (ADR), indicating that none of them is specific or complete. The present study reviews some of the established or commonly used CATs and its implications or relevance to dermatology in clinical practice.

Case processing in pharmacovigilance

Case processing is a systematic procedure that involves receiving information, case entry, duplicate check, reporting the case, triage, data entry & narrative writing, medical review, case closure and reporting ICSRs and aggregate. Fig. No: 1 representing the systematic pattern of case processing in Pharmacovigilance.

Basic steps in Pharmacovigilance Case Processing

Pharmacovigilance comprises of

•Safety data management
•Signal detection for any new altered safety issue
•Signal evaluation and making decisions with regard to safety issues
•Actions, including regulatory, to protect public health
•Informing all concerned parties or stakeholders

Safety Data Management

A Serious Adverse Event for a molecule could be generated during the preregistration or postmarketing phase. They could occur during clinical trials or be reported spontaneously by a patient, caregiver, relation, doctor, nurse or pharmacist. Another regulatory body or a licencee company could also be the informant. It could be received on phone, mail, fax, journals, newspapers or the latest social media.

Unexpected adverse events could arise anytime in the life of a product. These could put the user to serious risk and could curtail the life of the product. As part of the risk management plan, safety data is gathered throughout the life of a product. Consequently, every company that markets even a handful of products across many countries, gathers thousands of reports per year. The only way to manage this load is using latest software and automation.

The steps in safety data management are.

•Data collection and verification
•Coding of adverse reaction descriptions
•Coding of drugs
•Case causality assessment
•Timely reporting to authorities

Data Collection and verification.

Acknowledgement: A valid case needs to have four elements; an adverse event, a reporter, a patient and a drug. Every report needs to be acknowledged, more so the valid reports. Acknowledgement establishes a contact with the reporter for more information whenever required. It builds company image with the stakeholder and also protects from litigation. A consentious reporter may continue to send the same report repeatedly till it is acknowledged, hence this simple action avoids duplication.

Duplicate search: Due to, greater awareness, stringent regulations and multiple reporting sources, duplicate reports is a common phenomenon. Every safety management software has a facility to identify and delete duplicates. Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, clinical trial code, country, etc.) may be used to identify duplicate reporting. This action is of significance for further processing of the case. The duplicate could actually be follow up information that could alter the seriousness and hence reporting timeline of the case. Missed out duplicates could send misleading information to signal detection systems.

Coding of adverse reactions: This step ensures that everyone is talking the same language and the data can be shared internationally, Most commonly used system is the MedDRA(Medical Dictionary for Regulatory Activities). Use of MedDRA has lead to a global standardization across regulatory agencies, across companies & across countries. This step usually needs oversight by a medically qualified person.

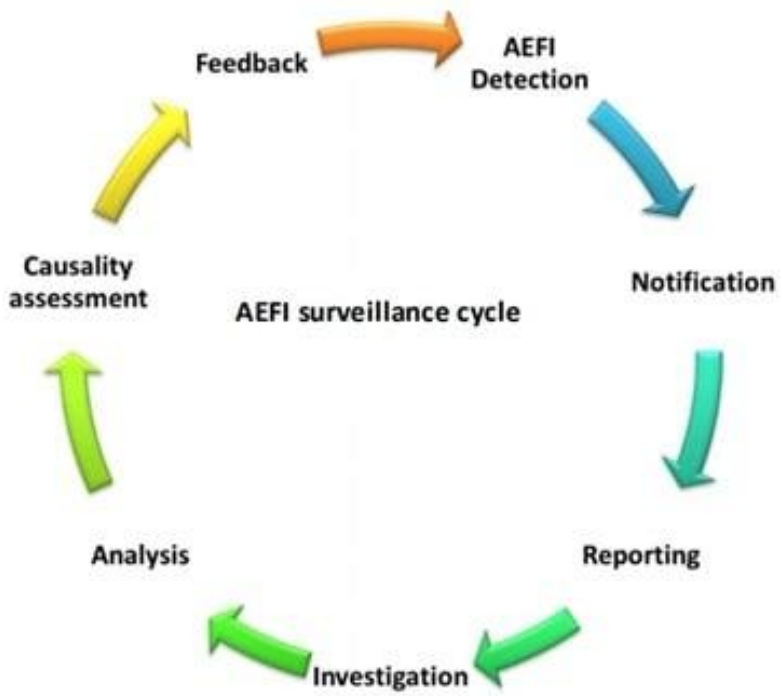
Coding for drugs: Both the suspect drug and concomitant medication have to be coded. The principle is again to be talking the same language across countries, companies and regulatory bodies. Most common dictionary is the WHO Drug Dictionary enhanced. This is provided as a product by the Upsala Monitoring centre of the WHO. Entries are updated 4 times a year. The majority of entries refer to prescription-only products, but some over-the-counter (OTC) preparations are included. The dictionary also covers biotech and blood products, diagnostic substances and contrast media. For chemical and therapeutic groupings the WHO drug record number system and ATC classifications are considered.

Adverse Events Following Immunization (AEFI)

As vaccine-preventable infectious diseases continue to decline, people have become increasingly concerned about the risks associated with vaccines. Furthermore,

technological advances and continuously increased knowledge about vaccines have led to investigations focused on the safety of existing vaccines which have sometimes created a climate of concern.Adverse event following immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. If not rapidly and effectively dealt with, can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence.

Alternatively, vaccine-associated adverse events may affect healthy individuals and should be promptly identified to allow additional research and appropriate action to take place. In order to respond promptly, efficiently, and with scientific rigour to vaccine safety issues, WHO has established a Global Advisory Committee on Vaccine Safety.



AEFI detection -To strengthen vaccine safety monitoring in all countries

Effective spontaneous reporting of adverse events following immunization (AEFI) is the first step to making sure that vaccine products are safe and are being safely administered. Yet almost half the world's population lives in countries without an effective system for monitoring the safety of vaccines.

Severe reactions following immunization are extremely rare so several countries have joined forces to pool their AEFI data in a common global database. The database is managed by the WHO Programme for International Drug Monitoring. Experience shows that most severe AEFI are not true vaccine reactions; rather, they are coincidental occurrences of health events or the anxiety associated with receipt of a vaccine.

The goal is that all countries should at least have a system for spontaneous reporting of AEFI and for investigating those that are serious. Countries that manufacture vaccines and countries where newly available vaccines are being introduced should have additional capacity for vaccine pharmacovigilance.

•SUSAR in Pharmacovigilance

A SUSAR is defined as an untoward and unintended response to a study drug, which is not listed is the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or.

SUSARs in the European Union

A SUSAR is defined as an untoward and unintended response to a study drug, which is not listed is the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

The responsibilities and requirements concerning SUSAR reporting are determined by Directive 2001/20/EC and a detailed guidance document ('CT-3').

An SAE that occurs during research with a medicinal product may be a SAR or a SUSAR. SAR is the abbreviation for Serious Adverse Reaction, and SUSAR for Suspected Unexpected Serious Adverse Reaction.

An SAE that occurs during research with a medicinal product is a SAR if there is a certain degree of probability that the SAE is a harmful and undesired reaction to the investigational medicinal product, regardless of the administered dose. If the SAR is unexpected it is called a SUSAR. In this case 'unexpected' means that the nature and severity of the SAR do not match with the reference safety information (RSI) as included in the SPC text or Investigator's Brochure.

SUSARs have to be reported to the reviewing MREC from the moment the dossier is submitted. This can be foreign SUSARs or SUSARs from the same medicinal product that occurred in a different study by the same sponsor if this information may have consequences for the safety of the research subjects in the study that is submitted for review.

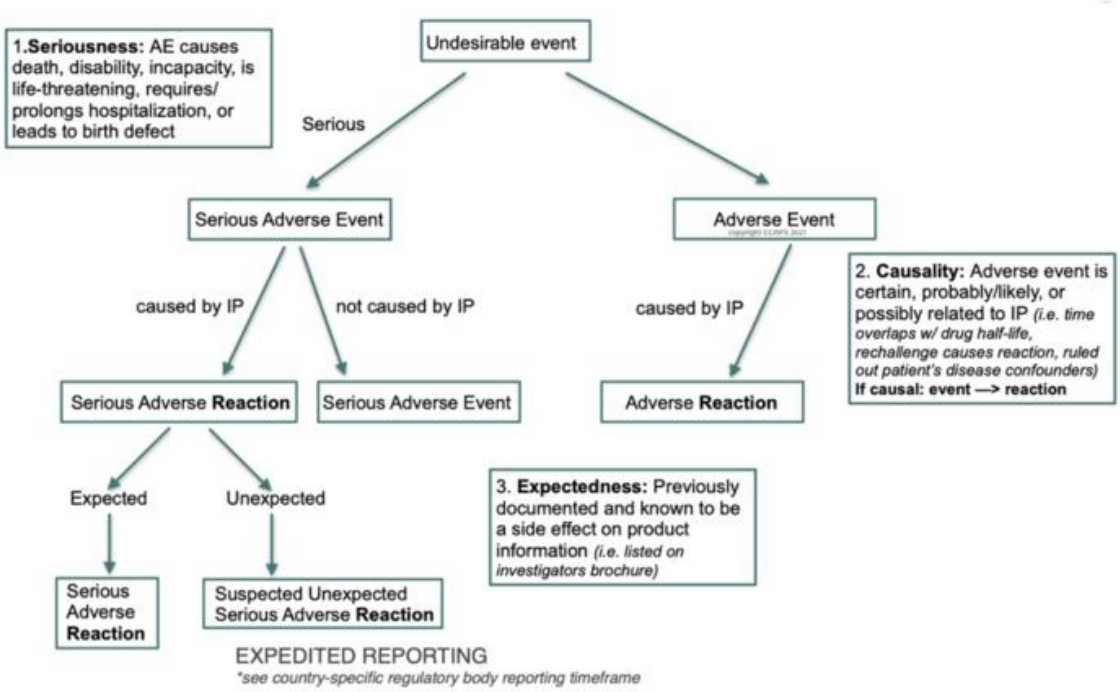
What is the difference between SAE and SusarSusar.

An SAE that occurs during research with a medicinal product is a SAR if there is a certain degree of probability that the SAE is a harmful and undesired reaction to the investigational medicinal product, regardless of the administered dose. If the SAR is unexpected it is called a SUSA.

A SUSAR that meets the seriousness criteria of life-threatening and/or results in death must be reported within seven (7) calendar days. A SUSAR that is not life-threatening or does not result in death must be submitted to the regulatory authorities within fifteen (15) calendar days.

Expedited Reporting

In the EU post-marketing environment, an Individual Case Safety Report (ICSR) may involve a serious or non-serious adverse reaction – regardless of expectedness. Such cases must be submitted to the regulatory authorities within 15 days or 90 days respectively. As a Marketing Authorisation Holder, you need to be fully versed in each change to the drug safety laws in concerned territories around expedited reporting as and when it happens. With regards to these updates, you as the Marketing Authorisation Holder need to implement them to remain fully compliant. With the right support, you can rapidly respond to the challenges in line with your Standard Operating Procedures.



Why Choose PrimeVigilance For Your Expedited Reporting

PrimeVigilance drug safety services consultants place particular emphasis on the timely reporting of post-authorization case reports. With a choice of fully validated E2B compliant safety database solutions (Argus Oracle Health Sciences Safety), highly effective SOPs and operating guidelines in place, thorough employee training, and a constant quality management system 'on time' reporting is a major priority. Reports may be made electronically or by hard copy as required by local regulations. PrimeVigilance may register and run electronic reporting systems such as EudraVigilance. Our EMEA-trained employees are there to ensure compliance with the rigorous requirements of such a system.

Career In Pharmacovigilance

Pharmacovigilance is required through the entire life cycle of a drug – starting at the preclinical development stage and going right through to continued monitoring of drugs once they hit the market.

Pharmacovigilance includes collecting, analyzing, monitoring, and preventing adverse effects in new drugs and therapies.

It can be broken down into three main sub-specialisms.
Surveillance: Surveillance is geared towards risk management and signal detection. Roles in this specialism focus analysis of drug safety information gathered from other professionals. Surveillance is responsible for creating development safety update reports (DSURs) for drugs in clinical research and periodic benefit-risk evaluation reports (PBRER) for drugs that are on the market.

Systems: Systems is concerned with the development of robust systems to store and manage data relating to pharmacovigilance. It involves keeping abreast of changing regulations and guidance in the pharmacovigilance industry and ensuring compliance at all levels of an organization.

Qualified Person for Pharmacovigilance (QPPV): Roles for individuals with vast experience who have demonstrated expertise in a particular discipline.

Operations: Operations focus on collecting and recording information during preclinical development, early clinical trials, and gathering real-world evidence (RWE) of adverse events reported by medical professionals and patients. Operations may also create standard operating procedures (SOPs), individual case study reports, and regulatory reports.

*** What pharmacovigilance officers do**

The exact nature of each role varies, but in essence, Pharmacovigilance Officers (PVs) collect adverse event data on drugs (Phase 4) to analyse and create usage warnings for the drug. Some roles insist on physicians, nurses, or those with a Master of Science degree. A Master's in pharmacovigilance is your best route into the industry – but that takes up to 2 years and is very expensive.

Responsible for conducting, monitoring or reporting regular pharmacovigilance developments and supervising the processes related to ensuring drug effectiveness and avoiding adverse effects or side effects of marketed pharmaceutical products among the general population in research trials and hospitals.

Typical responsibilities include

•recording and reporting adverse reactions received from healthcare professionals and consumers.
•conducting in-depth interviews with patients and healthcare professionals.
•developing a thorough knowledge of products.
•completing periodic safety update reports on drugs and other treatments.
•writing and reviewing serious adverse effects reports and forms.
•flagging up early warning signs of adverse effects of drugsminimising the risk of serious side effects.
•completing safety audits.
•working on clinical trials of new drugs.

Typical employers of pharmacovigilance officers

•Pharmaceutical companies
•Medical device companies
•Biotechnology companies
•Regulatory authorities

Vacancies are advertised online, by careers services, specialist recruitment agencies, in national newspapers and in relevant scientific publications such as The Pharmaceutical Journal, New Scientist, Science and their respective websites.

Qualifications and training required

To become a pharmacovigilance officer, you will need a degree. Most employers will ask for a relevant life science or pharmacy degree. It's also possible to get into this career as a qualified health professional, such as a nurse or pharmacist with relevant medical or nursing qualifications.

Pharmacovigilance Jobs

•Safety or Pharmacovigilance Physician (medical director, MD/MBBS, IMG)
•Safety Compliance Writer
•Good PV Practices manager
•GCP specialist
•Pharmacovigilance vendor
•Case processing specialist
•Clinical trial case processing safety specialist
•Post-marketing case processing safety specialist
•Epidemiology safety associate (MPH)
•Risk management manager
•Signal management specialist
•Periodic reporting specialist
•Regulatory affairs safety specialist

Education and Training on Pharmacovigilance at Regional Training Centers

A primary objective of NCC-PvPI is to promote the safest use of medicines through contributing to appropriate education in pharmacovigilance and training activities across the country. The NCC identified nine Regional Training Centers (RTCs) such as JSS Medical College, Mysore; Seth GS Medical College and KEM Hospital, Mumbai; Postgraduate Institute of Medical Education and Research, Chandigarh; Institute of Post Graduate Medical Education and Research, Kolkata; All India Institute of Medical Sciences, Bhopal; B. J. Medical College, Ahmedabad; Silchar Medical College

and Hospital; All India Institute of Medical Sciences, Rishikesh; and Nizam's Institute of Medical Sciences, Hyderabad. These centers provide continual training to the personnel at AMC of their respective regions.

CONCLUSION

ADRs reporting through PvPI improved with the measures such as education, training, and provision of technical assistance. The PvPI is a vital knowledge databases for Indian drug regulation. The PvPI plans to expand its scope of activities to widen its reach to other healthcare professionals and to strengthen measures for capacity building.

Although the medicines were launched in different decades, approaches to the ADR studies were similar for all three therapeutic cases: antibiotics, NSAIDs and SSRIs. Both descriptive and analytical designs were applied. Despite the fact that analytical studies rank higher in the evidence hierarchy, only the lower ranking descriptive case reports/spontaneous reports provided information about new and previously undetected ADRs. This review underscores the importance of systems for spontaneous reporting of ADRs. Therefore, spontaneous reporting should be encouraged further and the information in ADR databases should continuously be subjected to systematic analysis.

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