Review Article

Pharmacovigilance

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ABSTRACT

Pharmacovigilance started about 170 years ago, although it was not yet named as such at that time. It is structured activity in the professional health field, with important social and commercial implications aimed at monitoring the risk/benefit ratio of drugs, improving patient's safety and the quality of life. In this commentary we report the milestones of pharmacovigilance up to the present day, in order to understand all the steps that have characterized the historical evolution; from the first reports, which were essentially letters or warnings sent by clinicians to publishers of important and famous scientific journals, up to today's modern and ultra-structured electronic registries. The historical phases also help us to understand why pharmacovigilance helped us to achieve such important results for man's health and for pharmacology itself, and to identify the challenges that await Pharmacovigilance in future years.

Keywords: Adverse drug reactions, History, Legislation, Pharmacovigilance, Signal detection, Thalidomide, vaccine safety.

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INTRODUCTION

Pharmacovigilance is the science and activities related to detection, assessment, understanding and prevention of Adverse effect or any other medicine related problem [1].

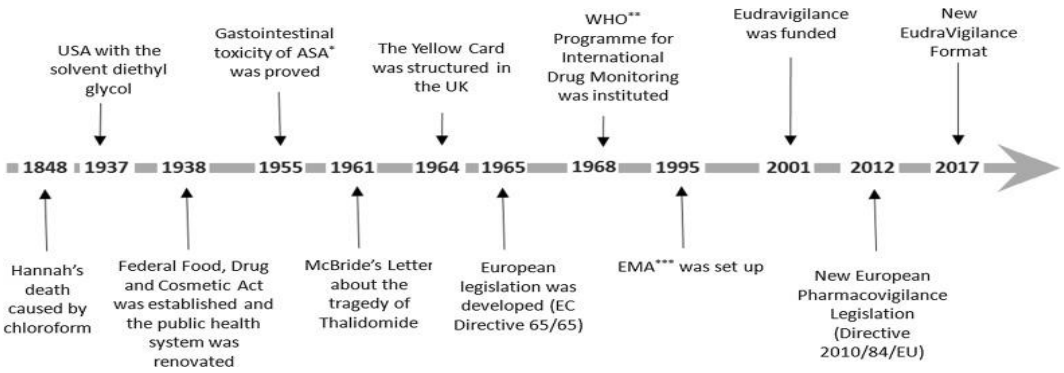
Objective

The aims of pharmacovigilance are to:

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions;
- Improve public health and safety in relation to the use of medicines;
- Encourage the safe, rational and more effective (including cost-effective) use of medicines; and
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public [1].

History

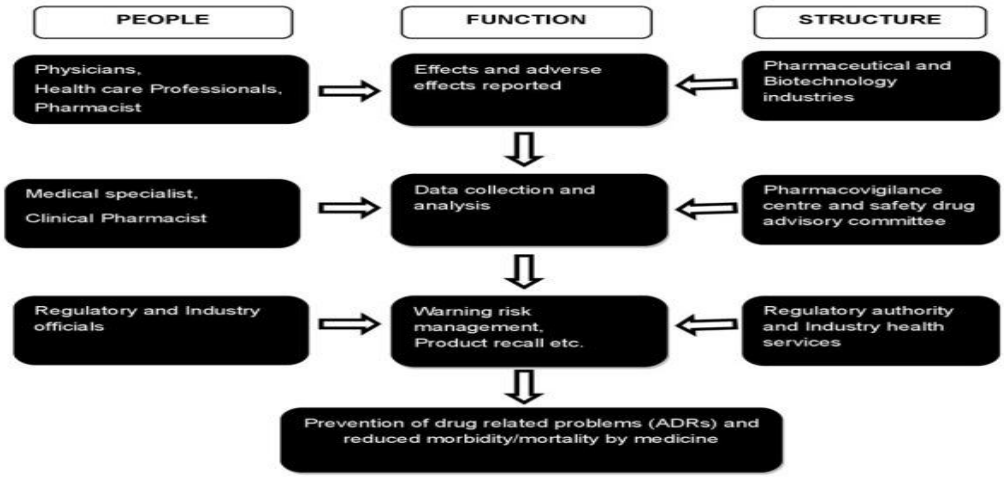
The history of Pharmacovigilance started 169 years ago on Jan 29, 1848, when a young girl (Hannah Greener) from the north of England died after receiving chloroform anaesthetic before removal of an infected toenail. Sir James Simpson had discovered that chloroform was a safer and powerful anaesthetic, and he had introduced it in clinical practice. [2].



- In 1961, a big change of European Pharmacovigilance happened following the tragedy of Thalidomide. Dr. McBride, an Australian doctor, wrote a letter to the editor of the Lancet Journal, in which he suggested a connection between congenital malformation of babies and thalidomide.
- In 1973, a retrospective study showed the correlation between the congenital malformations of babies and the ingestion of thalidomide during pregnancy. o Many studies of observed adverse drug reactions were conducted between 1968 and 1982 [3].
- In 1992, the European Society of Pharmacovigilance (ESoP) was funded, turned into the International Society of Pharmacovigilance (IsoP). The aims of this society were to promote Pharmacovigilance and enhance all aspects of the safe and proper use of medicines.
- In 1995, the European Medicines Agency (EMA) was set up. In 2001, Eudra Vigilance was funded. It is the official European database for managing and analysing information on suspected adverse reactions to medicines which have been authorized for the market or being studied in European clinical trials. [4]

Development

- The discipline of PV has developed considerably since the 1972 WHO technical report, and it remains a dynamic clinical and scientific discipline.
- It has been essential to meet the challenges of the increasing range and potency of pharmaceutical and biological medicines including vaccines, which carry with them an inevitable and sometimes unpredictable potential for harm.
- To fulfil the PV obligations for its marketed products as per regulations, a pharmaceutical company in India has to essentially carry out activities such as collection, and expedited reporting of serious unexpected ADRs.
- A typical setup for PV studies, including people involved on various levels, organizational units and their functions are shown in Figure [4].



Importance of safety monitoring of medicine

- Contribute to the assessment of benefits, uses, side effects, harm, effectiveness and risk of medicines.
- Assess the safety of drug therapies, especially recently approved drugs.
- Measures the economic impact of ADR prevention as manifested through reduced hospitalization, optimal and economical drug use, and minimized organizational liability.
- Provides updated drug safety information to health care professional and other stakeholders [5].

WHO International Drug Monitoring Programme

- Established in 1968, The WHO Programme for International Drug Monitoring (PIDM) provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals from data submitted to the WHO global individual case safety report (ICSR) database by member countries.
- The programme consists of a three-part network:
- National pharmacovigilance centres from WHO member countries are responsible for case reports sent to the WHO ICSR database (managed by the Uppsala Monitoring Centre (UMC) in Sweden),
- UMC oversees the WHO programme operations, including:
- Collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of drugs,
- Collaborating with member countries in the development and practice of pharmacovigilance,
- Alerting NRAs of member countries about potential drug safety problems via the WHO signal process.

- WHO headquarters in Geneva, Switzerland is responsible for policy issues [6].

Pharmacovigilance Program Of India (PvPI)

Pharmacovigilance Programme of India (PvPI) - Indian Pharmacopoeia Commission, Ghaziabad. The Pharmacovigilance Program of India (PvPI) was launched with a broad objective to safeguard the health of 1.27 billion people of India. Adverse drug Reactions (ADRs) are reported from all over the country to NCC-PvPI, which also work in collaboration with the WHO Programme for International Drug Monitoring (PIDM) and also contributes to the Global ADRs database. NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authority of India (CDSCO) in taking decision for safe use of medicines. The mission of the PvPI is to safeguard the health of the Indian population by ensuring that the benefit of the use of medicine outweighs the risks associated with its use. In 2017, the Pharmacovigilance Programme of India (PvPI) - Indian Pharmacopoeia Commission (IPC), in Ghaziabad, India, became a WHO Collaborating Centre [7].

Introduction to Adverse Drug Reaction

Definition: A noxious, unintended response to a drug that occurs at a normal dose used for prophylaxis, diagnosis and therapy of disease [8].

Classification

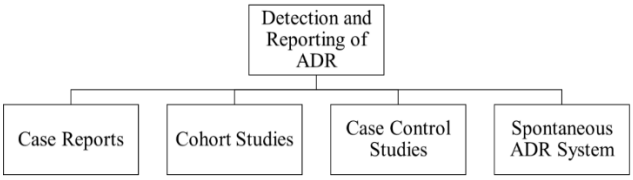
- On the basis of ABCDE:
  - Type – A,
  - Type – B,
  - Type – C,
  - Type – D,
  - Type – E,
  - Type – F.
- On the basis of onset
  - Acute,
  - Sub-acute,
  - Latent.
- On the basis of severity
  - Mild,
  - Moderate,
  - Severe [9]

Detection and Reporting of ADR

Physician has most important role to play in Pharmacovigilance. Not merely because he is the first person to whom the patient will come with symptoms; but also, to suspect an ADR. A healthcare professional or marketing authorization holder reports a suspected adverse drug reaction related to one or more medicinal products, to a national competent authority (Pharmacovigilance centre).

Reports are made in writing (e.g., using report forms), by telephone, electronically, or by any other approved way [10].

Reports are collected and validated by the Pharmacovigilance centre and are usually entered into a database.[11]



Causality assessment

Information on causality assessment presented in real time can improve the experience of ADR reporting, turning it into an engaging activity.

We believe that this network can be very useful to other pharmacovigilance centres, mainly to those that do not have access to a full-time expert to evaluate ADR reports.

As every method for ADR causality assessment has some advantages but also some limitations. Studies assessing the reliability of causality assessments concluded that 'no causality assessment method has shown consistent and reproducible measure of causality [13].

Management of 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 on-going safety trials. Such has been the case with antidotes for direct oral anticoagulant-induced bleeding [14].

Basic Terminologies Used in Pharmacovigilance

According to CIOMS, every National Pharmacovigilance Centres of WHO should follow the following criteria:

- The system should embrace the concept of one world-wide.
- It should have world-wide regulatory acceptance.
- It should contain clinically descriptive terminology.
- It should have appropriate categories and terminology so that:
  - One can derive easy labelling,

- Information a safety profile can be clearly presented it is appropriate for international pharmacovigilance,
- It is appropriate for pre-and post-marketing use.
- It can avoid the deficiencies in the current terminology.
- It should be developed with the assistance of medical and coding experts.
- It should provide authorized translations in major languages.
- If we can help to achieve these objectives, drug safety, as we know it, will become considerably more understandable [15].

Drug And Disease Classification

Anatomical, Therapeutic and Chemical Classification Of Drugs

- The Anatomical Therapeutic Chemical (ATC) Classification System is a drug that classifies the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) and was first published in 1976.
- In this system, drugs are classified into groups at five different levels:

First level

The first level of the code indicates the anatomical main group and consists of one letter. There are 14 main groups. Example: C - Cardiovascular system.

Second level

The second level of the code indicates the therapeutic subgroup and consists of two digits. Example: C03 - Diuretics.

- **Third level**
- The third level of the code indicates the therapeutic/pharmacological subgroup and consists of one letter. Example: C03C - High-ceiling diuretics.
- **Fourth level**
- The fourth level of the code indicates the chemical/therapeutic/pharmacological subgroup and consists of one letter. Example: C03CA - Sulphonamides.
- **Fifth level**
- The fifth level of the code indicates the chemical substance and consists of two digits. Example:C03CA01 - Furosemide.
- **ATC vet**
- The Anatomical Therapeutic Chemical Classification System for veterinary medicinal products (ATCvet) is used to classify Veterinary drugs.[16]

International classification of diseases

- The International Classification of Diseases is a globally used diagnostic tool for epidemiology, health management and clinical purposes. The ICD is maintained by the World Health Organization.
- It provides a system of diagnostic codes for classifying diseases.
- ICD defines the universe of diseases, disorders, injuries, it allows for easy storage, retrieval and analysis of health information for evidenced-based decision-making.
- ICD-10 has 21 chapters against 17 chapters in ICD-9 in which numeric codes were used, whereas alpha numeric coding has been adopted in ICD-10.
- The ICD -10 contains 21 chapters, and they are as follows:
- Chapters I to XVII – Diseases and other morbid conditions.
- Chapter XVIII – symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified.
- Chapter XIX – injuries, Poisoning and certain other consequences of external causes.
- Chapter XX – External causes of morbidity and mortality. Chapter XXI – Factors influencing health status and contact with health services.[17]

Daily defined doses

- The WHO's definition is: "The DDD is the assumed as average maintenance dose per day for a drug used for its main indication in adults.
- By applying DDD it is possible to:
- Examine changes in drug utilization over time.
- Make international comparisons.
- Evaluate the effect of an intervention on drug use.
- Document the relative therapy intensity with various groups of drugs.
- Follow the changes in the use of a class of drugs.
- Evaluate regulatory effects and effects of interventions on prescribing patterns.[18]

International nonproprietary names for drugs

- An international non-proprietary name (INN) is an official generic and Non-proprietary name given to a pharmaceutical drug or an active ingredient. INNs are intended to make communication more precise by providing a unique standard name for each active ingredient, to avoid prescribing errors.
- To provide health professionals with unique name and universally available designated name to identify each pharmaceutical substance.

- For clear identification, safe prescription and dispensing of medicines to patients.
- For communicating and exchange of information among health professionals and scientists worldwide.[19]

Drug Dictionaries and Coding in Pharmacovigilance

WHO Adverse Reaction Terminologies

- The WHO Adverse Reactions Terminology (WHOART) is a dictionary meant to serve as a basis for rational coding of adverse reaction terms. The system is maintained by the Uppsala Monitoring Centre (UMC), the World Health Organization Collaborating Centre for International Drug Monitoring.
- A subset of adverse reaction terms referring to OR possibly being indicative of serious diseased states, which has been regarded as particularly important to monitor.

MedDRA and standardized MedDRA queries

- Med-medical, D – dictionary- regulatory, A – activities.
- It is clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry.
- It provides Standardized communication between industry and regulators and to provide an international multi – lingual terminology.

Standardized MedDRA Queries

- These are the tools developed to facilitate retrieval of MedDRA coded data as a first step in investigating drug safety issues in Pharmacovigilance and clinical development.
- SMQs are validated and are grouped together after testing, discussion and they provide a strong tool for analysis and reporting.
- The following are a small sampling of SMQs that are available to users today: Anaphylactic shock, CNS disorders, Convulsions, Hypersensitivity.[19]

WHO Drug Dictionary

- WHO Drug Dictionary is a database with information about medicinal products from all over the world – it contains medicinal products and information related to them in a relational database system. Information is provided in a consistent and structured way. It provides useful groupings of data – useful for both data input and output. It is continuously updated.

WHO-DD

A source of international drug names:

- Substance names according to International Non-Proprietary Names (INN).
- Drugs classified according to the Anatomical Therapeutic-Chemical (ATC) classifications system.

Information on companies and reference sources.[20]

Eudravigilance medicinal product dictionary

- Eudravigilance is the European Union pharmacovigilance database and data-processing network (the 'EudraVigilance database').
- It supports the secure exchange, processing and evaluation of Individual case study reports (ICSRs) related to medicinal products authorised in the European Union (EU) and investigational medicinal products (IMPs) studied in clinical trials authorised in the EU, signal detection, evaluation and management.
- Proactive release of information on adverse reactions in compliance with personal data protection legislation in the EU.
- Electronic submission of information of medicinal products authorised in the EU.
- Provision of information on IMPs by the sponsor before completing a clinical trials application in the EU.
- Main components are:
  - Eudravigilance (EV) gateway,
  - Eudravigilance Post-Authorization Module (EVPM),
  - Eudravigilance Clinical Trial Module (EVCTM),
  - Extended Eudravigilance Medicinal Product Dictionary (XEVMPD),
  - Eudravigilance Data Analysis System (EVDAS),
  - Adrreports.eu portal.

Information Resources in Pharmacovigilance

Basic drug information resources:

- Drug information is current, critically examined, relevant data about drugs and drug use in a given patient or situation.
- Current Information uses the most recent, up-to date sources possible.
- Critically Examined Information should meet the following criteria:
  - More than one source should be used when appropriate.
  - The extent of agreement of sources should be determined.
  - The plausibility of information, based on clinical circumstances.
  - Relevant Information must be presented in a manner that applies directly to the circumstances under

consideration (e.g., patient parameters, therapeutic objectives, alternative approaches).[8]

- Some of the basic drug information resources are:

Primary Resources

Primary literature is the most up-to-date resource available to the clinician and consists of journal articles reporting original research, new ideas, or opinions. These resources are useful for research, education, and current awareness.

Secondary Resources

Secondary resources include indexing and abstracting systems that organize and provide easy retrieval of primary resources. Indexing systems include the article citation, with or without access to the abstract; some include a link to the full-text article. Examples of secondary resources include MEDLINE (through PubMed, EBSCO, Ovid), Academic Search Premier, Cochrane Database of Systematic Reviews, Iowa Drug Information Service (IDIS), International Pharmaceutical Abstracts (IPA), Embase/ExcerptaMedica, Biosis Previews/Biological Abstracts, CancerLit, SedBase, Reactions, Clin-Alert, Current Contents, and Toxline. Proper training is required for efficient use of these resources.

Tertiary Resources

Tertiary resources are sources that condense and summarize data from the primary literature. These include not only textbooks and compendia but also electronic databases (e.g., Micromedex, Lexicomp) and review articles. The best tertiary resources are written by experts in the field and are peer reviewed. If the tertiary resource is not current or comprehensive, a secondary resource should be consulted to locate primary literature on the topic.

Others

Internet sources of DI like search engines (Boolen Logic, Advanced search keywords, Medline mesh terms), Libraries, Research associations, Government bodies, Information centre in Industries, Analyst labs, Poison Centres etc. [21]

Specialized resources for adverse drug reactions

- Standard reference books on adverse effects such as Meyler's Side Effects of Drugs, the Side Effects of Drugs Annuals (SEDA), Martindale: The Complete Drug Reference, Davies Textbook of Adverse Drug Reactions and the papers they summarize.
- Regulatory authorities may issue safety alerts for a variety of commercial products based on information submitted to them by the manufacturer (which have not been published or made available elsewhere). Examples of safety bulletins can be found.
- Specialist drug information databases such as full-text databases (e.g., Pharma news feed and Iowa Drug Information Service (IDIS), bibliographic databases (e.g., Derwent Drug File, TOXLINE, Pharmline) and referenced summary databases (e.g., Drugdex, XPhram).
- However, review authors will have to consider the subscription costs to these specialist databases, particularly as their usefulness or additional yield have yet to be formally evaluated in the systematic review setting.[22]

Establishing Pharmacovigilance Programmes

Establishing in a Hospital & Operation of Drug Safety Department in Industry

Pharmacovigilance centers

It is center of expertise for the art and science of monitoring and analysis of drug. It should be set up with the approval of the authority responsible for the regulation of medicines ("regulatory authority").Its function within the regulatory authority, a hospital, an academic institution or as an independent facility such as a trust or foundation.

Basic steps in setting up a pharmacovigilance center

- Make contacts with the health authorities, and with local, regional or national institutions and groups, working in clinical medicine, pharmacology and toxicology outlining the importance of the project and its purposes.
- Design a reporting form and start collecting data by distributing it to hospital departments, family practitioners etc.
- Produce printed material to inform health professionals about definitions, aims and methods of the pharmacovigilance system.
- Promote the importance of reporting adverse drug reactions through medical journals, other professional publications, and communication activities.
- Maintain contacts with international institutions working in pharmacovigilance, e.g., the WHO Department of Essential Drugs and Medicines Policy (Geneva), and the Uppsala Monitoring Centre, Sweden.
- Financial Requirements: Infrastructure, Human resource, Communication, Operational expenses.[23]

Contract Research Organization (CRO's)

- A Contract Research Organization, also called Clinical Research Organization (CRO) is a service organization that provides support to the pharmaceutical and biotechnology industries in the form of outsourced pharmaceutical research services.
- CROs are designed to reduce costs for companies developing new medicines and drugs in niche markets.

- CROs that specialize in clinical-trials services can offer their clients the expertise of moving a new drug or device from its conception to FDA/EMA marketing approval, without the drug sponsor having to maintain a staff for these services.[23]

Establishing a national programme:

- The National Pharmacovigilance Programme was officially inaugurated by the Honourable Health Minister Dr. Anbumani Ramadoss on 23 November 2004 at New Delhi.
- The National Pharmacovigilance Programme for India, sponsored by the World Health Organization (WHO) and funded by the World Bank, became fully operational in January 2005.
- The Programme aims to foster the culture of ADR notification in its first year of operation and subsequently aims to generate broad based ADR data on the Indian population and share the information with global health-care community through WHO-UMC.
- The nationwide programme, sponsored and coordinated by the country's central drug regulatory agency – Central Drugs Standard Control Organization (CDSCO) – to establish and manage a data base of Adverse Drug Reactions (ADR) for making informed regulatory decisions regarding marketing authorization of drugs in India for ensuring safety of drugs.
- Under the program 26 peripheral centres, 5 Regional centres and 2 zonal centres were established.
- The Peripheral centres will record the Adverse Events (AE) and send to the regional centres.
- They in turn collate and scrutinize the data received from the Peripheral centres and submit to the Zonal centres.
- The Zonal centres will analyse the data and submit consolidated information to the National Pharmacovigilance Centre.
- The Zonal Centre will also provide training, general support and coordinate the functioning of the Regional Centre.[24]
- **Vaccine Safety Surveillance**

Vaccine Pharmacovigilance

- The goal of vaccine pharmacovigilance is the early detection and timely response to adverse events following immunization, in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of population.
- Although vaccines are considered to be medicines with anti-infective activity that work by immunological action and administered for prophylaxis, pharmacovigilance for vaccines should be different from other drugs.
- Safety of vaccines, therefore, must be excellent to make it acceptable, since it usually has a deferred individual benefit, but immediate adverse drug reactions (ADRs).[25]

Vaccination failure

Vaccine-related (host-related)

- Immunodeficiency,
- Age-related maturation and senescence of immune responsiveness,
- Insufficient or suboptimal immune response,
- Interference due to other infectious agents,
- Waning immunity,
- Pre-existing infection with pathogen targeted by the vaccine or immunization during incubation period
- Immunosuppressive therapy.

Vaccine Related

- Vaccine is not 100% efficacious against included antigens,
- Incomplete coverage of strains, serotypes, genotypes, antigenic variants or escape mutants that can cause a vaccine-preventable disease,
- Antigenic interference or other vaccine-vaccine interactions in case of co-administered vaccines,
- Manufacturing-related (e.g., batch variations).

Usage Issues

- Administration error,
- Vaccination series incomplete, non-compliance with recommended schedule, including lack of recommended booster vaccination(s),
- Storage-related (e.g., cold chain),
- Vaccine beyond expiry date when used.

Immunization-related issues

- Suboptimal recommendations regarding number and time points of primary and/or booster vaccinations,
- Shortage of vaccine leading to no or incomplete vaccination,
- Confirmed clinical vaccine failure.
- The occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization. [26]

Adverse Event Following Immunization

- 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. [25]

Pharmacovigilance methods

Passive surveillance

Spontaneous reporting

Recording and reporting clinical observations of a suspected ADR with a marketed drug is known as spontaneous or voluntary reporting. Spontaneous reporting of adverse drug reaction and adverse events is an important tool for gathering the safety information for early detection, case reports collected by such system represent the source of information providing the lowest level of evidence and highest level of uncertainty regarding casualty.

Case Series

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome.

Stimulated Reporting

Stimulated adverse event reporting in the early post-marketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population. This should be regarded as a form of spontaneous event reporting, and thus data obtained from stimulated reporting cannot be used to generate accurate incidence rates but reporting rates can be estimated.

Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program.

Senitel Site

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system.

Drug Monitoring Site

In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.

Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion.

Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross sectional studies:

Cross-Sectional Study (Survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies are best utilized when exposures do not change over time.

Case-Control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or

using data collected specifically for the purpose of the study of interest.

Cohort Study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time.

Targeted Clinical Investigation Studies

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamics and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.[26]

Communication in Pharmacovigilance

Effective communication in pharmacovigilance

- The active, timely and effective communication plays a major role in issuance of updates on guidelines on drug safety as per pharmacovigilance experts present in all around the world.
- Effective communication helps in creation of safety guidelines with the following statements:
  - The safety information on all the drug molecules must be sufficiently collected, assessed and made easily accessible to all by each country.
  - Drug safety information must be able to improve health of the community.
  - Health care providers and public must be educated regarding appropriate use of drug molecules along with safety information.
  - Free access to all the evidence required to assess and understand risks and benefits of drug.
  - Information and remedies are efficiently communicated.
  - These factors will definitely help in generation of drug safety guidelines and evaluation of risk vs. benefits ratio of drug molecules.[26]

Communication in drug safety crisis management

- Gathering intelligence for medicine and drug safety from:
  - Manufacturers,
  - Regulators.
  - Employees,
  - Health professionals,
  - Pharmacists,
  - Academics, etc.
- Crisis Planning:
  - Assess risks,
  - Produce plans,
  - Define roles and responsibilities,
  - Appoint crisis management team,
  - Draw up communication plan,
  - Produce contact and organization chart,
  - Promote crisis-ready culture,
  - Publish plans and conduct training,
  - Test, review and practice.
- Communication plan: Core elements are:
  - Identifying audiences (Who?)
  - How communication is to take place (How?)
  - What messages are to be communicated (What?)
  - The core process is: Active, two-way communication
- The ideal spokesperson should be:
  - Polite and patient,
  - Well-informed and authoritative,
  - Accurate and reliable,
  - Articulate,
  - Available,
  - Trustworthy.[27]

Communication with regulatory agencies, business partners, health care facilities and media

- During the development of an innovative healthcare product, early and effective communication with your regulatory agency is essential to achieve a complete and robust regulatory submission and streamline the review process.

- Generally, a company should consider interacting with the agency at certain stages of product development to exchange ideas on program status and planning (for example, before the initiation of a clinical trial or the submission of a marketing application*).
- Omissions of significant data in a regulatory submission may lead to the agency's refusal to file the application, additional data being requested (that is, not achieving first-cycle approval), the submission not being approved or cleared by regulatory agency, or the application being voluntarily withdrawn by the company.
- Product development should be a collaborative effort on the part of both the healthcare industry and the regulatory agency.
- Although the primary responsibility for product development (especially its identification, design and execution) lies with the healthcare industry, it is important to communicate the development plan to the regulatory agency and discuss any specific issues early on in the development phase.
- Such interactions allow critical issues to be discussed and resolved, bringing clarity to the agency's expectations on submission requirements. [28]

Safety Data Generation

Pre-clinical phase

- Within the Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example: Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.),
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.),
- Drug interactions,
- Other toxicity-related information or data.
- If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.[29]

Clinical phase

- Global pharmaceutical companies have found India's clinical research space and opportunity very attractive.
- India born CROs were able to offer the advantages of understanding the Indian scenario better, provide services at more competitive costs, and having better knowledge of Investigator sites in the country compared to the newer entrants in the market.
- India's existing favourable regulatory framework and regulations with international standards, increasing awareness of good clinical practice guidelines and its implementation by clinicians are some of the main reasons propelling the growth of clinical research in India.
- Some of the advantages that India offers as clinical trials destination are as follows:
  - High degree of compliance to international guidelines such as the ICH GCP and the regulations lay down by the US Food and Drug Administration.
  - Availability of well qualified, English speaking research professionals including physicians.
  - Ongoing support and cooperation from the government.
  - Lower cost compared to the west.
  - Increasing prevalence of illnesses common to both developed and developing countries.[30]

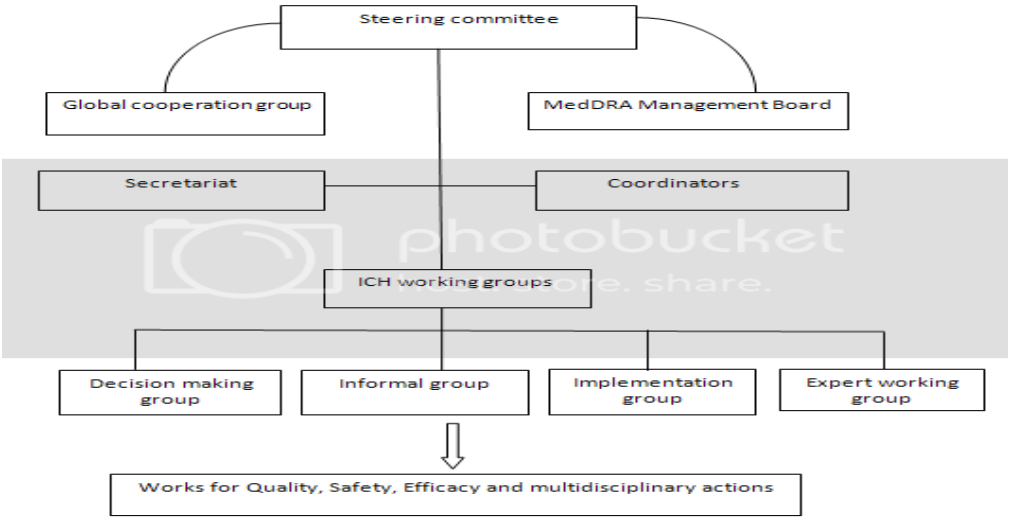
Post Approval Phase (PMS)

- PMS is based on the core principle that patient health and patient safety are critical factors to be considered when manufacturing and marketing pharmaceutical products.
- PMS fulfils the post-approval requirements of assessing and monitoring the potential risks associated with the use of pharmaceutical products in a larger patient population. In addition to potential risks, hitherto unknown adverse reactions can also be recognized during the PMS of drugs.
- PMS keeps in view the needs and goals for patient safety in current times, which crucially included centralized access to reliable and accurate drug product safety data.[31]

ICH Guidelines for Pharmacovigilance

Organization of ICH

The organizational structure of ICH consists of the following components:



ICH Steering Committee

Responsibilities

The ICH Steering Committee (SC) is the main organization which is involved in the following works:

- Govern ICH,
- Determines the policies and procedures for ICH.
- Selects topics for harmonization.
- Monitors the progress of harmonization initiatives.[32]

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. A Marketing Authorization should be fully versed in each change to the drug safety laws in concerned territories around expedited reporting as and when it happens.

Individual Case Safety Reports

An Individual Case Study Report (ICSR) is a safety service document which includes information required for reporting the adverse events and problems related to products and complaints filed by consumers with respect to any product. It is an important facet of adverse event reporting which is a source of data in PV (pharmacovigilance). The ICSR is most commonly associated with PV. To build a compliant ICSR, there are four elements which must be mentioned:

- A diagnosed patient,
- A reporter,
- A suspect drug,
- An adverse event.[33]

Periodic Safety Update Reports

A Periodic Safety Update Report (PSUR) is a pharmacovigilance document intended to provide an update of the worldwide safety experience of a medicinal product to regulatory authorities at defined time points post-authorization. Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSURs include:

- Data from clinical and non-clinical studies,
- Spontaneous reports (e.g., on the marketing authorization holder's safety database),
- Product usage data and drug utilization information,
- Observational studies, including registries,
- Scientific literature.[34]

Post Approval 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 Authorization 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. Including the responses, you need to introduce to remain fully compliant. With the right support you can rapidly respond to the challenges in line with your Standard Operating Procedures.[35]

Pharmacovigilance plan

- Summary of Ongoing Safety Issues At the beginning of the Pharmacovigilance Plan a summary should be provided of the:
  - Important identified risks,
  - Important potential risks,
  - Important missing information.

- This is important if the Pharmacovigilance Plan is a separate document from the Safety Specification. 3.1.2 Routine Pharmacovigilance Practices Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a Pharmacovigilance Plan.
- This routine pharmacovigilance should include the following: Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; The preparation of reports for regulatory authorities:
  - Expedited adverse drug reaction (ADR) reports,
  - Periodic Safety Update Reports (PSURs),
  - Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities,
  - Other requirements, as defined by local regulations. [36]

Good clinical practice in pharmacovigilance

- GCP is defined as a standard for the design, conduct, performance, and monitoring, auditing, recording, analysis and reporting of clinical trials or studies.
- GCP compliance provides public assurance that the rights, safety and well-being of human subjects involved in research are protected.
- It improves trial methods.
- Clinical trial concept better understood.
- Public/Political Concern over Safety Aspects.
- Itprotects the rights, safety and welfare of humans participating in research.
- Itassures the quality, reliability and integrity of data collected.
- Good Clinical Practice = Ethics + Quality Data.[37]

Pharmacogenomics of adverse drug reactions

Genetic related ADR with example focusing pk parameters

- Although the field of pharmacogenetics is not entirely new, there has been a marked increase in the number of studies evaluating associations with various ADRs.
- Numerous genetic associations have been made for immediate drug reactions, but to date, none appear robust enough to make clinical recommendations based on pharmacogenetics data alone.
- In contrast, studies have been able to demonstrate that for carbamazepine and abacavir, screening for specific HLA alleles can reduce the risk of severe delayed drug reactions.
- With advances in genotyping technology, discovery of additional clinically important risk alleles for drug allergy are very likely.
- Pharmacogenomics will certainly play a role in the new era of precision medicine.
- Whether broad-based pharmacogenetic testing will be ready for ‘‘primetime’’ in most patients seems unlikely in the near future.
- Sir William Osler is noted to have said, “The first duty of the physician is to educate the masses not to take medicine.”
- Pharmacogenomics offers the hope of tailoring that message to identify those patients who are most vulnerable, whereby recommending avoidance of a specific medicine is truly in their best interest.[38]

Drug safety evaluation in special population

Pediatrics

- The result of these legislative and regulatory policies has been a significant increase in paediatric studies and labelling changes and the quality of the information submitted.
- The safety studies conducted for paediatric patients are generally much smaller than those conducted for adult patients.
- This limited evaluation demonstrates that paediatric safety information cannot be predicted from adult safety information and supports including larger numbers of paediatric patients in safety trials.
- Smaller numbers of paediatric patients in drug safety trials compromises signal detection and the certainty that can be attached to any particular signal.

Pregnancy and Lactation

- Birth defects, still birth and deaths are a harrowing experience for both women and their families.
- The safe use of medication during pregnancy is an unmet medical and societal need.
- There is little information available to determine the risks to both mother and child.
- Approximately 90% of medications currently have no information about their potential to cause birth defects.
- Most medicine have not been tested in pregnant women.
- New drugs come out faster than information on lactation safety.
- Many studies have only small samples of breastfeeding mothers.

Geriatrics

- Methods to improve safe use of medications in elderly should be a multidimensional and multidisciplinary approach.
- This should start from the point of patient visit and should be an ongoing process involving all steps of drug use, and frequently revisited for individual patients.
- Prescribing step needs to be refined and more cautiously approached while prescribing in geriatrics patients.
- Safer use of the drugs can be promoted with appropriate education of patient, monitoring for adverse effects and frequent review for any drug interactions.
- Appropriate history taking is a vital step and equally challenging due to various inherent difficulties in this age group.
- Targeting high risk older adults has to be implemented as it is not practically possible to have an extensive approach for all the patients visiting the practitioners. [40]

Centre for International Organizations of Medical Sciences (CIOMS)

CIOMS Group:

- The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949.
- CIOMS Initiatives and Uptakes by ICH:
  - CIOMS I,
  - CIOMS IA,
  - CIOMS II,
  - CIOMS III,
  - CIOMS IV,
  - CIOMS V,
  - CIOMS VI
- CIOMS represents a substantial proportion of the biomedical scientific community through its member organizations, which include many of the biomedical disciplines, national academies of sciences and medical research councils.
- CIOMS mission is to advance public health through guidance on health research and policy including ethics, medical product development and safety.
- CIOMS is in official relations with WHO and is an associate partner of UNESCO.

CIOMS Form

This form provides a standardized format for the reporting of suspected adverse reactions to any particular medical product. It has proved of enduring value in practice since the 1980s and continues to be widely used. [40]

CDSCO (India) and Pharmacovigilance

Drug And Cosmetic Act

Schedules are divided alphabetically and named also alphabetically like Schedule A, Schedule B etc. till Schedule Y. Schedule Z is proposed but not implemented yet. Schedules are important part of Drug and Cosmetic Act 1940 & Rules, 1945. Every schedule contains specific information as discussed below:

- Schedule A: Contains various forms and formats of letters for applications of licensing etc.
- Schedule B: Contains fees structure for government-run labs.
- Schedule C: Contains various biological products and their regulation. Examples: Serums, Adrenaline Vitamins etc.
- Schedule D: List of drugs exempted from the provision of import of drugs.
- Schedule E: Contains various poisons and their regulation. Examples: SarpaVisha (Snake venom), Parada (Mercury) etc.
- Schedule F: This contains regulations and standards for running a blood bank.
- Schedule F-I: This contains regulations and standards for vaccines.
- Schedule F-II: This contains regulations and standards for surgical dressing.
- Schedule F-III: This contains regulations and standards for umbilical tapes.
- Schedule F-F: This contains regulations and standards for ophthalmic ointments and solutions.
- Schedule K: Contains various substances and drugs and their corresponding regulation.
- Schedule M: Contains various regulations for manufacturing, premises, waste disposal and equipment.
- Schedule N: Contains various regulations and requirements for a pharmacy.
- Schedule O: Contains various regulations and requirements for disinfectant fluids.
- Schedule P: Contains regulations regarding life period and storage of various drugs.
- Schedule P-I: Contains regulations regarding retail package size of various drugs.

- Schedule Q: Contains a list of permitted dyes and pigments in soap and cosmetics.
- Schedule R: Contains various regulations and requirements for condoms and other mechanical contraceptives.
- Schedule S: Lists various cosmetics and toiletries and directs the manufacturers of cosmetics to conform to the latest Bureau of Indian Standards requirements.
- Schedule T: Contains various regulations and requirements for manufacture of Ayurvedic, Siddha and Unani products.
- Schedule U: Contains various regulations and requirements for record keeping.
- Schedule V: Contains standards for drug patents.
- Schedule Y: Contains requirement and guidelines for clinical trials.

Schedule-Y: It is the requirements and guidelines for permission to import and/or manufacture of new drugs for sale or to undertake clinical trials.

Rule	Permission for
122 A	To import New drugs
122 B	To manufacture New drugs
122 D	To Import or Manufacture fixed dose combinations
122DA	To conduct clinical trials for New Drug/Investigational New drug
122 DAA	Definition of Clinical Trial

Requirements and guidelines on clinical trials for importing and manufacturing of new drugs

- Application for permission,
- Clinical Trials,
- Studies in specific formulation,
- Post marketing surveillance,
- Special studies: BA/BE studies. [41]

Differences in Indian and global pharmacovigilance requirements

Pharmacovigilance and India

In 1986, India proposed Adverse Drug Reaction Monitoring System (ADR monitoring System). It had 12 regional centres. India joined World Health Organization WHO-ADR Monitoring Programme in1998. In 2004-08, India had started National Pharmacovigilance Programme which was performing under 2 Zonal, 5 regional and 24 Peripheral Regions. Currently India is having Pharmacovigilance Programme of India which has commenced from 2010.

ADR Reporting Procedure of India:	ADR Reporting procedure of USA:
In India Reporting of ADR is done through following three ways under PvPI: 1. Healthcare Professional 2. Consumer Reporting 3. Public Health Programme-PHP The reports are recorded through ADR reporting form by ADR monitoring center /National Co-ordination Centre. Then they are entered into the vigiflow software and reports re-checked for its completeness. The access of report in vigiflow creates WORLWIDE UNIQE NUMBER.AMC personnel ensure the completeness and quality of the report and Causality assessment is done by Centre Co-Ordinator/Deputy Co-Ordinator. Technical assessment is performed and follow-up is also done. Hard copy as well as soft copy is preserved and their access is restricted.	In USA, Adverse Drug Reactions are reported according to the Post Marketing Reporting of ADRs to US Food and Drug Administration and FDA submit the Reports to the FDA Adverse Event Reporting System-FEARS. Reporting of ADR is done through following ways: Healthcare Professionals (Physicians, Pharmacists, Nurses and Others), Consumers (Patients, Family Members, Lawyers and Other), Regulated industries, Facility Users. Healthcare professionals, consumers, Regulated Industry and User facilities record the ADRs through either ADR form 3500A or ADR form 3500B and send these reports to FDA. Reporting is done online through MadWatch. FDA sends ADRs report to FDA Adverse Event Reporting System. Reports are assessed by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). If a probable safety concern is acknowledged by FAERS, supplementary evaluation is performed this evaluation might include conducting studies using other large databases. The records are maintained for 10 years. [42]

CONCLUSION

Pharmacovigilance is essentially based on the qualitative and quantitative study of spontaneous adverse drug reactions reports, followed by a clinical assessment/judgment with regards to its impact on the overall safety profile of the drug. It is particularly useful for identifying potential safety signals of a rare adverse event or in orphan disease settings where exposure data are limited prior to marketing. The purpose of pharmacovigilance is to enhance patient care and patient safety in relation to the use of medicines according to the life cycle of a health product. Furthermore, pharmacovigilance can support public health programs by providing ongoing data throughout a product's life cycle allowing for an accurate, reliable, and balanced

assessment of the risk–benefit ratio of the product as more and more data becomes available with its use in the market.

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