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Pharmacovigilance- A drug safety monitoring tool

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ABSTRACT

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Introduction: Pharmacovigilance is a science that ensures patient safety against both newly launched and well-established medicinal products in the market. Pharmacovigilance is considered a specific tool used for observing and estimating Adverse Drug Reactions (ADRs) and is essential for successful drug management programs, clinical trials, and public health programs.
Objectives: The objective of this narrative review is to converse about drug safety, global pharmacological authorities and their responsibility, the process of adverse event reporting, and the main functions of pharmacovigilance.
Methods: In the few past years, the number of reported ADRs got increased as a result of which the volume of data got increased. To handle such huge data and the need to understand the pharmacovigilance, it requires highly skilled and proficient people for immediate detection of drug's side effects and protects the product from improper removal.
Results: The existing global network of pharmacovigilance centers will be strengthened through an independent review process in coordination with the Uppsala Monitoring Center. Its main role is to assess trials and crucial issues of drug safety that probably influence public health beyond national borders. In this global arena, Pharmacovigilance becomes an important and integral part of clinical research.
Conclusions: Most of the countries set up pharmacovigilance centers to monitor drug safety; however, millennial pharmacovigilance faces major challenges for improved safety and drug monitoring.

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Introduction

Pharmacovigilance (PV) has developed as a scientific tool for testing the safety and efficacy of drugs and other medical products. Following World Health Organization, Pharmacovigilance is the medical science and activities associated with the recognition, testing, estimation, and prevention of side effects or any other drug-related problems (WHO, 2004). It is considered a vital and constitutive part of clinical research and drug development. The present review summarizes the aspect of pharmacovigilance and converses about drug safety, the process of adverse event reporting, and its future consideration in healthcare sectors. This review highlights the 3 main PV functions i.e., case management, signal management, and benefit-risk management, and also provides insights about the role of different pharmacological bodies helpful in creating the understanding of drug safety profiles for further improvement in patient safety.

Drug reliability and pharmacovigilance persist in an effective clinical and scientific approach. With the CDSCO ban on certain major drugs such as pioglitazone and tegaserod, pharmacovigilance has now become a necessary tool for evaluating drug safety profiles. It is very vital in

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new medicines because the data obtained from clinical trials are deficient to address all characteristics of drug safety. However, despite all their advantages, evidence continues to find the most serious, but often preventable, side effects of illness, the cause of illness, disability, and even death. To prevent or reduce risk to patients and therefore improve public health, methods for monitoring and assessing drug safety in clinical practice are essential (Jeetu G and Anusha G, 2010; Wal P. *et al.,* 2015).

WHO perceptions for Drug Safety Monitoring

The pharmacovigilance centers are set up in more than 65 countries in 2002. The Uppsala Monitoring Center (UMC) managed the WHO membership in International Drug Monitoring. Pharmacovigilance is now definitely rooted in sound scientific principles and combines good clinical practice. Discipline requires continuous improvement to meet the expectations of society as well as the needs of global health. The Sixteenth World Health Assembly adopted a resolution (WHA 16.36) (Geneva, 1973) that affirmed the need for primary action regarding the rapid distribution of evidence related to adverse drug reactions. This also results in the establishment of the WHO Pilot Research Project for International Drug Monitoring. The basis of this center is to establish a system, which operates internationally to recognize earlier unknown or poorly assumed adverse drug reactions, there is a need. **(**van Grootheest *et al.,* 2004**)**

Pharmacovigilance: Past and Present

The evolution of Pharmacovigilance was largely from a record-keeping function – intending to ensure the processing and presentation of individual case safety reports and overall reports − to the existing, where it currently focuses proactively on identifying safety issues and take steps to reduce or mitigate the risk to patients. This evolution has been particularly rapid since the early 2000s (Jacob.D *et al.,* 2013)

There are numerous obligations to protect and promote public health through testing and monitoring of prescription drugs for human consumption. This is done by regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). (European Medicines Agency, 2021)

The functions of these regulatory agencies came out more than a century ago with a focus on consumer protection and patient safety. In the early 1900s, the FDA (Bureau of Chemistry) enforced food regulations that cause a global health problem than contaminated or illegal drugs. However, the Food, Drug, and Cosmetic Act of 1938 brought cosmetics and medical equipment under control, and drugs were required to be labeled with appropriate guidelines for safe use. (US Food and Drug Administration, 2021) Amendments to this law have allowed the FDA to continuously improve its ability to protect public health by regulating the use of prescription drugs.

In 1995, the EMA was established as a designated body of the European Union (EU). The primary function was to manage the safety and support of community and animal health via observation in addition to surveillance of drugs for human and animal use. The EMA can be regarded as the base of a medicine set-up in Europe involving more than 40 national authorities such as the European Commission, the European Parliament, and many other EU structures. The Agency operates in partnership with its European partners to develop the greatest European drug management system and to safeguard the citizen's health (European Medicines Agency, 2021)

Adverse Event Reporting System

While performing a clinical trial, reporting of any adverse event is compulsory in a clinical trial site whereas in post-market surveillance adverse event reporting is largely voluntary. As such, under-reporting of post-market events is a well-known incident. Although it is hard to estimate, the aggregate under-reporting rate in automated reporting systems may exceed 90% (Hazell L and Shakir SA, 2006). One of the main reasons for poor reporting is that majority of reporters consider that there is no requirement for reporting an adverse drug reaction that is previously identified and easily recognized. In case of doubt that a drug has caused or contributed to the side effects, there is a need to report the adverse events. In absence of complete reporting, the accurate incidence of adverse drug reactions cannot be completely recognized. There is a strong necessity for uplifting awareness and encourage the reporting of adverse events so that the healthcare industry can abundantly examine and recognize the possible safety problem. Very complex and significant relationships exist between the wide variety of associates involved along with the performance of assessing drug safety. Such associates should collectively expect, realize and respond to the growing needs and opportunities of communities, health managers, strategy managers, officials, and health workers.

WHO Monitoring Center

This Center established a system through which it controls the world database of aggregate reports collected from nationalized institutions (Olsson S, 1998). It has developed limited reportage by every Nationalized Institutions, thus interaction is easier among nations for encouraging instant signals detection.

Safety and Quality Assurance

This department functions to assist in saving souls and progress healthiness via ending the massive gap among the possible power provided by basic medicines and truth that of millions of people, especially the poor as well limited access, medicines are not available, are not expensive, unsafe or misused (WHO Medicines Strategy, 2003)

Nationalized Pharmacovigilance Set-ups

A very significant role has been played by National PV Centers in building community understanding of the safety

of the drug. However, the progress is limited as numerous nationalized and local institutions were located in the health center, medical institutes, or toxic and drug info centers, not in the drug control organization. The majority of institutions within industrialized nations have started effective monitoring systems by documentation and prescription event monitoring (PEM) methods to gather evidence-based data on side effects to certain medications. Certain programs had begun to be executed in the United States of America, the United Kingdom, New Zealand, and Sweden. The total expense of the pharmacovigilance program in comparison to the nationalized cost of drugs or ADR costs to the nation is very small. (Coulter DM, 2000; Mackay FJ, 1998).

Healthcare Professionals

Initially, the physicians were the only authorities invited to record as a judgment that a disease or drug creates a specific symptom through the ability to diagnose separately. Today, various groups of healthcare experts will identify several types of medicines-related issues (Hall *et al.,* 1995; Hornbuckle *et al.,* 1999). Many clinicians found it difficult to report an adverse event especially when various observed events are considered normal or "expected."

Patients

It is the patient who recognizes the true advantage and risk of a drug received. If the patient is involved directly in reporting medicine-related issues, this will add up the proficiency of the pharmacovigilance system as well as balance out the faults of systems built on records provided by healthcare experts only. Additionally, results reported by patients (i.e., one associated with self-diagnosis and lacking medical prescribing) are the further possible trace of data to identify adverse drug reactions (Banerjee AK and Ingate S, 2012). Pharmacovigilance structure has been presented in **Figure 1**.

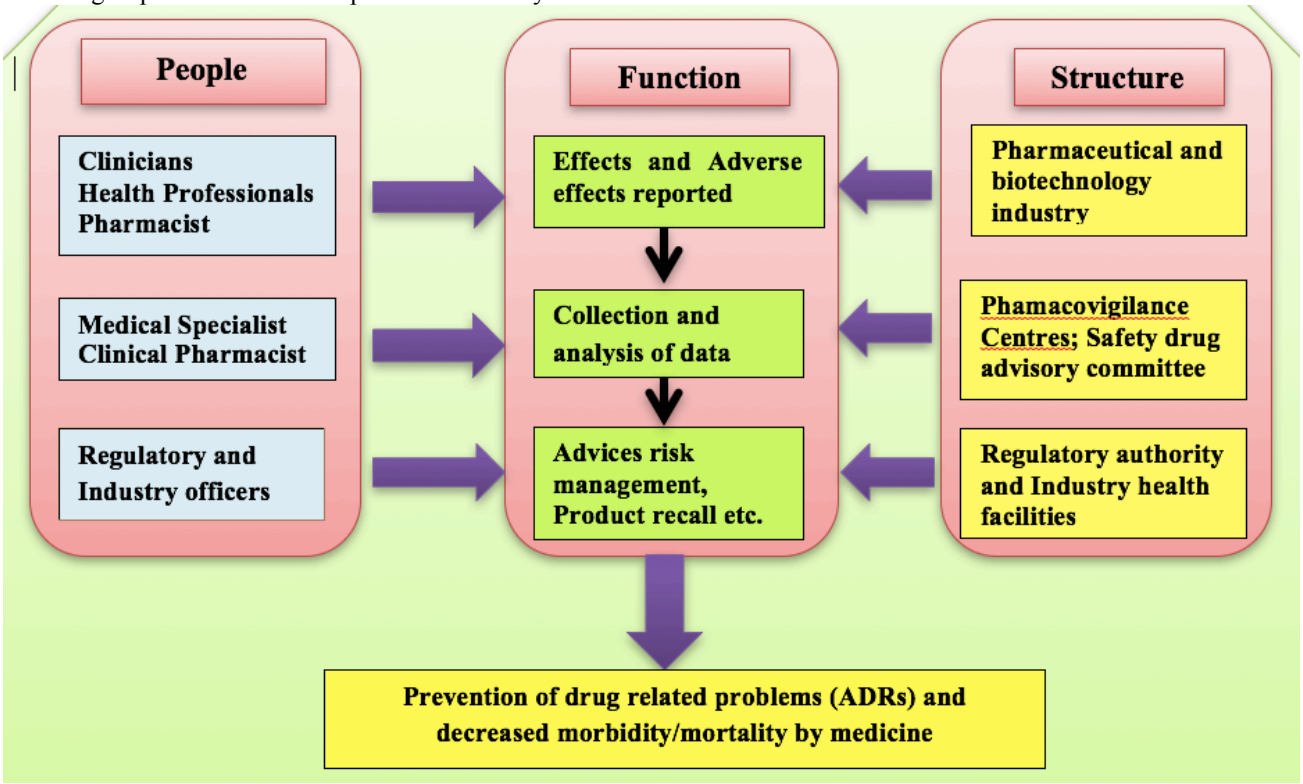


Figure 1. Pharmacovigilance: A structure outlook

Overview of Pharmacovigilance functions

Pharmacovigilance has 3 core functions i.e., case reporting, signal detection, and benefit-risk ratio. To figure out the relation of these activities with one another, it will be helpful to observe them from a strategic view (Figure 2).

In a fundamental, public administrative plan, there will be 3 main elements: input, process, and output (Paul Beninger, 2018). In the case of a pharmacovigilance structure, a databank is a principal, "process," necessary for all fundamental actions. Starting through a databank, it is a record for all patient safety information about the products of a pharmaceutical company; i.e, its medicines, remedies, injection, medical equipment, compound products, and in vitro diagnosis. Such information will help to identify the reporter and patient (e.g., human characteristics, associated diseases), specifies the medication involved (e.g. dosage, dosage, duration, other complementary medications), and details of a traumatic event that has been reported (e.g. duration, complications, hospitalization. hospital). Whatever information the company is aware of, the regulations define a systematic and formal order of

information for timely reporting. In the beginnings of pharmacovigilance operations, the databank was a self-effacing, hand-operated worksheet; Over the years, it progressively evolved towards an automated, programmed worksheet, and finally acquired its modern shape as an infomercial, extremely efficient, committed databank (Oracle, 2017; Bioclinica, 2017). Additionally to specific firms that store so much data, supervisory authorities as well keep a record of vast information related to adverse event reports from organizations with products permitted in their dominions which regularly receive >1 million records for each year.

Progressing towards the "input", in those initial period the safety clinician was very much determined to be trained by the Council for International Organization of Medical Sciences (CIOMS) on how to obtain information on adverse event reportage forms (CIOMS Form I, 2021) and placed in a databank with a regular, systematized, and judicious manner for compliance necessities. The objective has demanded a comprehensive international system of processing which derived to the fore as a function of the Medical Directory (MedDRA) for ICH Regulatory Activities (MedDRA, 2018). The area of Case reporting has been developed from such activities.

Subsequent progressing towards the "output", asking the database in the first phase to solve center (corporate) and peripheral (usually supervisory) security queries remained a temporary, inconstant, and extremely varying procedure restricted for accessible usage of the original information. In the preliminary 2000s, retailers expanded their skills regimen extensively, and the Systematized Policies of MedDRA were launched (Introductory Guide for Standardised MedDRA Queries (SMQs), 2018) to perform a wide variety of growing databank examinations. The area of Signal detection has been developed from such activities.

The benefit-Risk ratio is the final part of this program. The section is a complete method used to address all product information related to the risk that is designed and evaluated as combined case reporting and signal detection functions afterward puts it concerning outcome's profits (EMA. Benefit-risk Methodology, 2021).

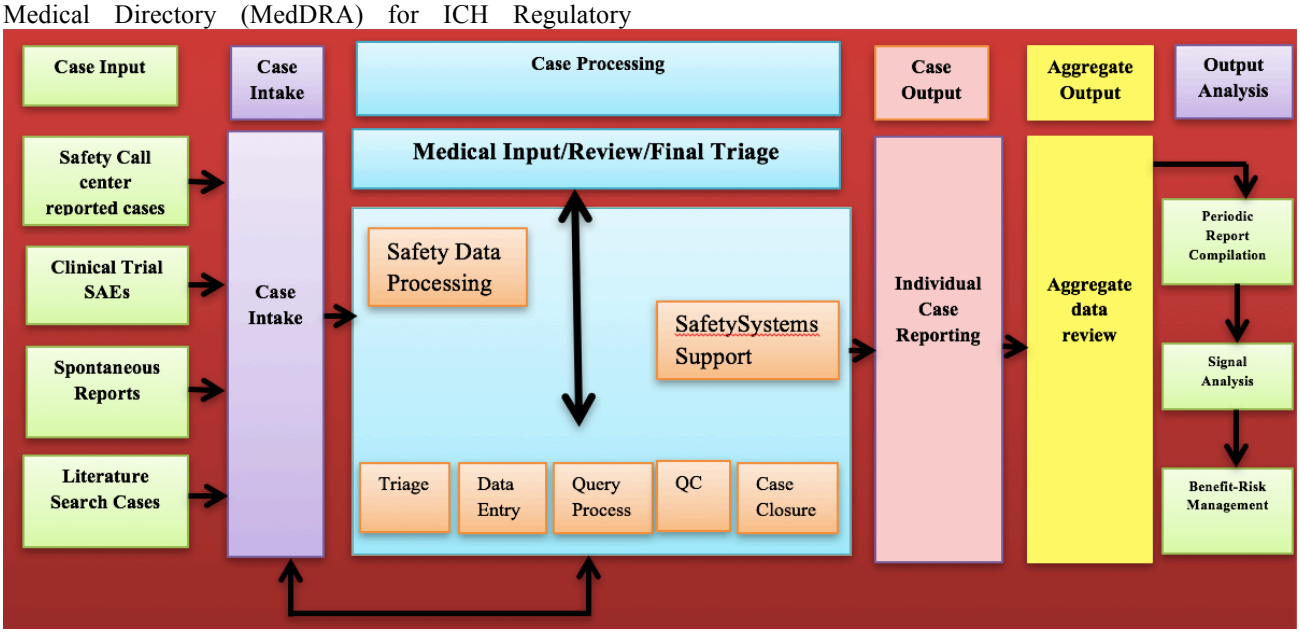


Figure 2: Overview of Pharmacovigilance activities

Pharmacovigilance along with Global healthiness

The present worldwide system of PV set-ups administered by the WHO Monitoring Center is possibly supported through self-regulating review organizations. The primary objective of such an organization is to address crucial and essential problems related to drugs safety which may adversely distress community well-being across nationalized borders. The Erice Declaration plays a critical role concerned with communication in drug safety and offers an agenda for ethics and procedure aimed at the assortment, examination as well as further transmission of problems related to drugs safety. In the present era, despite advances in pharmacovigilance, the public health burden of ADR remains significant (Lazarou *et al.,* 1998). Pharmacoeconomic research on expenses of harmful events shows that governments are disbursing more money from the health budget to address the associated costs **(**White *et al.,* 1999**).** However, there is well-defined information on drugs safety which is in direct association with social, governmental, financial, and traditional aspects of access to medicines, their use, and public opinion **(**Avorn J and Solomon DH 2000; Ball *et al.,* 1998**).**

Utilization of Drugs: Drug use policies exist as a principal element of medicinal care. For example, injecting drug usage remains very customary for unindustrialized lands **(**Bapna *et al.,* 1996**).** Direct advertising to users about recommended drugs has commonly developed within numerous nations. Such informative evidence allows

patients to take particular medicinal decisions exclusive of the assistance of a clinician or pharmacologist. The result has been an increase in self-medication, licensing, and the illegal sale of drugs over the Internet, as well as over-prescribing via doctors on patients' demand. This significantly affected the prescribing (Kane *et al.,* 1999; de Vries *et al.,* 1999). These public health programs can be used not only to focus on patients but are also beneficial for the community. In the context of creating awareness and informative programs, it must consist of the population of adolescents and the adults in addition to highly assisted in collaboration through the mass media, schools, administrative organizations, and non-administrative institutes. The Programs via Uppsala Monitoring Centre stand entirely upon the cooperation of nationalized PV institutions. In an ideal world PV, set-ups should be present in all countries. **(**Jeetu G and Anusha G, 2010**)**

The global response towards problems related to drugs safety

Some welfare concerns possess universal influence through possible adverse effects on the community. In such cases, there is a requirement for comprehensive global review as well as reaction. There is a formation of an autonomous counseling board of multidisciplinary therapies reinforced by WHO. This board includes clinical pharmacists, education administrators, academics, and infectious diseases. The work of this panel is to collaborate with the WHO member countries and thereby advise the WHO on safety issues related to pharmaceutical products, including the International Drug Monitoring Center **(**Vaccine Safety Advisory Committee, 1999**).**

Discussion

The main responsibility of PV performed is to tackle the questions presented using growing distance next to the potential of medications, entirely had the predictable and somewhat unexpected ability to cause harm. As soon as harmful effects and toxic effects arise, particularly where they were not known previously, it is important to report and analyze this information and effectively inform the audience. In all medicine, the benefits-risk ratio must be balanced out. Risk minimization ensures the appropriate usage, safety, and efficacy of medications. It also considered the patient's potentials and interests during treatment decisions. During the last few years, actions of PV changed dramatically since engaged in recording each case study towards further active situation over some time, containing signal recognition and risk minimization actions. Although experimental studies permit an organization for understanding the drug's preliminary safety report, it's the post-market surveillance that facilitates framing a drug's complete benefit-risk report in a real-world context.

Conclusions

Pharmacovigilance is a scientific tool used for collecting, identifying, and evaluating the risk of adverse drug reactions. The major activity of PV is the assessment of the benefit-risk ratio of drugs to provide better safety and efficacy for patient's well-being. This review summarized objectives and methodologies used in PV with a critical overview of pharmacovigilance activities and different associates involved in such a system.

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Conflict of interests

The authors declare that there is no conflict of interests

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