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A Brief Review on Pharmacovigilance

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Abstract: Pharmacovigilance is an important and integral part of clinical research. Pharmacovigilance is "defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines. Here the main focus on the aims and role of pharmacovigilance in medicines. Pharmacovigilance has been regarded as a type of continual monitoring of unwanted effects and other safety-related aspects of drugs, which are already placed in markets. The pharmacovigilance has been known to play an important role in rational use of drugs, by providing information about the adverse effects possessed by the drugs in general population. The present review presents in brief about the relevance, need, functioning, role, and importance of pharmacovigilance.The main objective of review is to unfold various aspects of pharmacovigilance

Keywords: Pharmacovigilance, Adverse Drug Reactions, Drug safety

Abbreviations:

- **ADRs:** adverse drug reactions
- **BMI:** body mass index
- **CPRD:** clinical practice research datalink
- **FDA**: Food and Drug Administration
- **GP:** general practitioner
- **ICH :** International Council for Harmonisation of Technical Requirements for Pharmaceutical Use
- **WHO:** World Health Organisation

I. Introduction:

Pharmacovigilance has been described as "the science and activities relating to the detection, assessment, understanding and prevention of the adverse effects of drugs or any other possible drug-related problems. It is a fundamental component of effective drug regulation systems, public health programmes and clinical practice" , Pharmacovigilance supports safe and appropriate use of drugs by a) promoting the detection of previously unknown ADRs and interactions and increases in frequency of known ADRs, b) identifying risk factors for the development of ADRs and c) estimating quantitative aspects of benefit/risk analysis and disseminating information to improve drug prescribing and regulation [1]

A century-long history of many tragic events has played a critical role in shaping the present-day drug development structures and processes, none more so than those concerned with pharmacovigilance (PV). It describes the core PV functions of case management, signal management, and benefitrisk management. It also covers the breadth of scope of safety-related activities that a present-day pharmaceutical company must be prepared to manage, most of which are likely to reside in a department charged with PV responsibilities.[2]

Acording to the World Health Organization, "Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem, particularly long term and short term adverse effects of medicines".Pharmacovigilance is also known as Drug Safety and abbreviated PV or PhV. The etymological roots for the word "pharmacovigilance" are: Pharmakon (Greek word for 'drug') and vigilare (Latin word for 'to keep watch'). Pharmacovigilance greatly focuses on adverse drug reactions (ADRs) which are defined as any reaction to a drug which is harmful and unintended including lack of efficacy used for the prophylaxis, analysis or therapy of illness or for the modification of physiological function[3]

Pharmacovigilance (PV) with its ultimate goal of minimising risks and maximising the benefits of medicinal products serves as an important public health tool . The World Health Organization (WHO) defines PV as "the science and activities relating to the detection, assessment,

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understanding and prevention of adverse effects or any other drug related problem, Prior to approval by regulatory authorities, drug products are required to undergo extensive testing and rigorous evaluation during clinical trials, to establish their safety and efficacy , The rationale for post-marketing PV is based on the need to mitigate the limitations of pre-marketing/registration clinical trials including small population sizes, a short length of time and the exclusion of special population groups (e.g. pregnant women and children) . Therefore, unexpected or severe adverse drug reactions (ADRs) are often not identified before regulatory approval resulting in increased morbidity, mortality and financial loss [4]

Harmful reactions that are caused by the intake of medication are known as Adverse Drug Reactions (ADRs) and the activities relating to the detection, assessment, understanding and prevention of adverse effects attributable to prescription drugs are referred to as pharmacovigilance, Pharmacovigilance begins during clinical trials and continues after the drug is released into the market. Due to the various limitations of clinical trials, it is not possible to fully assess the consequences of the use of a particular drug before it is released . Adverse reactions caused by drugs following their release into the market is a major public health problem: with deaths and hospitalizations numbering in millions (up to 5% hospital admissions, 28% emergency visits, and 5% hospital deaths), and associated costs of about seventy-five billion dollars annually drugs is of paramount importance for drug manufacturers, national bodies such as the U.S. Food and Drug Administration (FDA), and international organizations such as the World Health Organization (WHO[5]

Government agencies, like the FDA or the European Medicines Agency (EMA), have expanded their pharmacovigilance efforts in various ways. In the U.S., post marketing surveillance of drugs occurs actively and passively. Methods to accomplish this include Phase IV clinical trials, in addition to voluntary and mandatory reporting through the FDA's Adverse Event Reporting System (FAERS), MedWatch, and the Institute of Safe Medication Practices Medication Error Reporting System (MERP) . The MedWatch program, for example, allows the public (patients and providers) to report ADRs which they suspect or observe ,While it is mandatory for manufacturers to report adverse events, reporting by healthcare professionals and the public is voluntary. Due to the voluntary nature of these systems, reporting and detection of adverse events may not be timely and is incomplete. Recent research has exposed the various inadequacies of spontaneous reporting systems, prompting researchers to explore additional sources for ADR monitoring [9,2,10]. These systems, for example, suffer from under-reporting, over-reporting of known ADRs, incomplete data, duplicated reporting, and unspecified causal links. Various additional techniques have been utilized for post marketing monitoring of ADRs, including retrospective chart analysis, prospective surveillance, and information extraction from electronic health records, clinical narratives and case reports. These approaches have their own associated challenges. For example, electronic health records generally face challenges associated with the pervasiveness of confounding variables, and the definition and ascertainment of exposures and outcome[5]

The first governmental organization of pharmacovigilance was created in 1938 with the foundation of the Federal Food, Drug and Cosmetic Act, after more than 100 deaths had occurred in the United States of America because of the use of sulphanilamide elixir, containing diethyl glycol as the solvent . The new organization foresaw that the safety of drugs should be demonstrated before their market approval, and introduced the possibility of conducting factory inspections. In Europe, the creation of the government pharmacovigilance systems awaited the tragedy of thalidomide. In the 1950s, thalidomide was used in pregnant women as an antiemetic sleeping drug. It is only in 1961 that 2 physicians (Dr McBride in Australia and Dr Lenz in Germany) first suggested the teratogenicity of this drug after observing an abnormally high number of new born children with phocomelia [1—3]. In 1973, a retrospective study confirmed the association between the congenital malformations of babies and the ingestion of thalidomide during pregnancy [6]

Since 1980s, the missions and activities of pharmacovigilance have been insistently including: collecting and managing data on the safety of medicines, looking at individual case reports to detect new ''signals'', proactively managing drug safety to minimize any potential risk associated with the use of medicines, communicating and informing healthcare professionals and patients , To this end, pharmacovigilance is based on causality assessment analysis (e.g. immutability), i.e. seeking for establishing the causal link between an (adverse) drug reaction and the medicinal product[6]

Pharmacovigilance plays a key role in assessing, monitoring and preventing adverse drug reactions (ADRs) . ADRs have a high clinical, social and economic cost as they can result in risk to life

and having to stop taking an effective drug therapy, and a requirement for additional medical interventions and use of health services, with long hospitalizations . Although randomized clinical trials are considered the gold standard for the evaluation of the efficacy and safety of drugs , the design of such trials includes small and homogeneous populations monitored for short periods, making it difficult to detect many drug-related reactions . Thus, the detection and reporting of suspected ADRs in clinical practice are the backbone of post market surveillance . Current pharmacovigilance systems have been able to identify many major safety issues, even though their functions and methods leave considerable room for improvement . These systems comprise, among other mechanisms, spontaneous reporting (SR) . The main purpose of the SR system (SRS) is the early detection of new, rare and serious ADRs and it has the advantage of covering the entire population in a cost-effective way . The SRS has weaknesses, of which the most important is under-reporting; it has been estimated that only 6% of all ADRs are reported. Under-reporting delays the detection and identification of safety problems, making it more difficult for health authorities to act and preserve public health [7]

Pharmacovigilance programs in the next 10 years, describe in brief the potential implications of such trends on the evolution of the science. These days pharmacovigilance is facing lots of challenges to develop better health care systems in this global pitch[15]

In an earlier paper, we retraced the history of pharmacovigilance, with some views to its future . Five years later, the world has changed a little. In addition to traditional spontaneous reporting by healthcare professionals, patient reporting has become mainstream. The use of social media has exploded, and is being mined in the hope of possibly identifying new safety issues ,Data resources such as countrywide healthcare systems databases have become readily available, and hospital based data repositories or electronic health records are opened new possibilities[8]

As the use of herbal medicines has increased, so too have the reports of suspected toxicity and adverse events. Such unwanted reactions can be due to (i) side effects (usually detectable by pharmacodynamics and often predictable); (ii) reactions occurring as a result of overdose, over duration, tolerance, dependence-addiction (detectable either by pharmacodynamics or pharmacovigilance), (iii) hypersensitivity, allergic and idiosyncratic reactions (detectable by pharmacovigilance), (iv) mid-term andlong-term toxic effects including liver, renal, cardiac and neurotoxicity also genotoxicity and teratogenicity (detectable by in vitro and in vivo toxicological studies or by pharmacovigilance). As many herbal products on the market have not been thoroughly tested for their pharmacology and toxicology, pharmacovigilance has paramount importance in detecting unwanted reactions [10]

The GVP (Guidelines on good pharmacovigilance practices; module VI) recommend tracking some “special situations”: Pregnancy and breast-feeding (is necessary to follow the outcome of the pregnancy and the development of the newborn); paediatric population or older [(or populations provided for in SPC (Summary of Product Characteristics)]; lack of therapeutic efficacy, a major failure of the product in the achievement of the pharmacological waiting for an approved indication (e.g., treatment failure, poor response, patient does not respond to medication, no results with the drug, etc.)increasing scientific, regulatory and public scrutiny is focused on the obligation of the medical community, pharmaceutical industry and health authorities to ensure that marketed drugs have acceptable benefit–risk profiles. This is an intricate and ongoing process that begins with careful preapproval studies, but continues after regulatory market authorisation when the drug is in widespread clinical use. In the latter environment, surveillance schemes based on spontaneous reporting system (SRS) databases are a cornerstone for the early detection of drug hazards that are novel by virtue of their clinical nature, severity and/or frequency. Pharmacovigilance is often used to describe the aforementioned surveillance activities [12]

The goal of pharmacovigilance is to assess the risk of adverse events for patients taking drugs—bearing in mind that no medicine is completely safe—at the time of approval for sale and throughout the product’s lifecycle. Although pharma co vigilance is essential to both patients’ safety and clinical outcomes, there are some disease states for which early, accurate, and detailed reporting is crucial. Oncology treatments—with high toxicity and narrow therapeutic windows—fall into this priority category. However, studies on pharmacovigilance and post-marketing surveillance of cancer drugs are scarce. Although pharmacovigilance is defi ned in many ways by different systems, ultimately, its aims are to enhance patients’ care and safety and to provide reliable and balanced information for effective assessment of the risks and benefits of medical drugs. WHO sets the

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global standard, defining pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem".2 In 2010, 134 countries were part of WHO's pharmacovigilance programme, which is promoted through collaboration between the Programme for International Drug Monitoring and the Collaborating Centre for International Drug Monitoring.[13]

In the current regulatory environment, where efficacious drugs are brought to market as soon as possible , post-marketing drug surveillance (PMS) has become increasingly important in order to characterize cost-effectiveness and harm in real practice. Recent examples of drug withdrawals, due to uncommon ADEs after millions of patients were exposed , have reinforced the inadequacy of current methods of PMS.[14]

Patient-centeredness is defined as "health care that establishes a partnership among practitioners, patients, and their families (when appropriate) to ensure that decisions respect patients' wants, needs, and preferences, and that patients have the education and support they need to make decisions and participate in their own care Recently, patients' perspectives were incorporated into pharmacovigilance (PV) activities such as ADR reporting, signal detection and evaluation, risk management, medication error assessment, benefit–risk assessment and risk communication . This review focuses on the participation of patients in reporting ADRs[20]

Implementation of this abbreviated approval pathway for biosimilars adds to the need for collection and analysis of safety data after approval through effective post-approval safety surveillance systems that accurately track and trace all biologics from the patient to the manufacturer. This ongoing surveillance, known as pharmacovigilance, refers to all scientific and data-gathering activities related to detecting, assessing, understanding, preventing and communicating any potential or identified safety problems associated with a product, including a biosimilar[22]

➢ **History of Pharmacovigilance in India**

Pharmacovigilance in India started from 1986. A formal Adverse Drug Reactions (ADR) monitoring system was initiated with 12 regional centres, each covering a population of 50 million. However, no noteworthy growth was made. Afterward in 1997, India joined the World Health Organization (WHO) and Adverse Drug Reaction (ADR) scrutinizing program based at2 Uppsala, Sweden but got fail. Hence, after 2005 WHO supported and World Bank – funded National Pharmacovigilance Programme (NPPV) of India was made operational [3]

➢ **Need of pharmacovigilance**

The forceful marketing of new drug products by pharmaceutical companies and the consequential rapid disclosure over a short period of time of large numbers of patients to them necessitate the formation of a system for global assessment of drug safety concerns. These actions need an effective and efficient pharmacovigilance system that has been realized more than ever to make sure safe use of drugs. There are several rationales for increasing requirement of pharmacovigilance system.

The bases of need are as follows:

A. Untrustworthiness of pre-clinical safety information.

- Well-controlled environment.
- Appropriate and precise sample size.
- Pressure from various systems to decrease time to authorization.

B. Altering pharmaceutical marketing policies.

- Aggressive marketing
- Launch the drug in many countries at a time

C. Varying physician's, patient's and other health professional's preferences

- Increasing use of newer drugs
- Increasing use of drugs to get better quality of life
- Shift of manage to self-administered treatment.

D. Easy convenience

- Growing conversion of prescription drugs to over the counter drugs
- Easy access to drug information on the Internet

➢ **Classification of pharmacovigilance**

According to International Conference on Harmonization Efficacy Guidelines 2 (ICHE2E) guidelines pharmacovigilance techniques can be categorized as:

- **Passive surveillance**

1. Spontaneous reporting system (SRS).
2. Case series. Stimulated reporting

- **Active surveillance**

1. Sentinel sites
2. Drug event monitoring

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3. Registries

- **Comparatives observational studies**

1. Cross sectional study
2. Case control study
3. Cohort study

- **Targeted clinical investigations**

1. Descriptive studies
2. Natural history of disease
3. Drug utilization study [3]

➢ **Pharmacovigilance techniques can be also classified as hypothesis generation techniques and hypothesis testing techniques as follows:**

A. Hypothesis generating techniques

1. Spontaneous ADR reporting
2. Prescription event monitoring

B. Hypothesis testingtechniques

1. Case control study
2. Cohort studies
3. Randomized controlled trials [3].

Process flow of PV

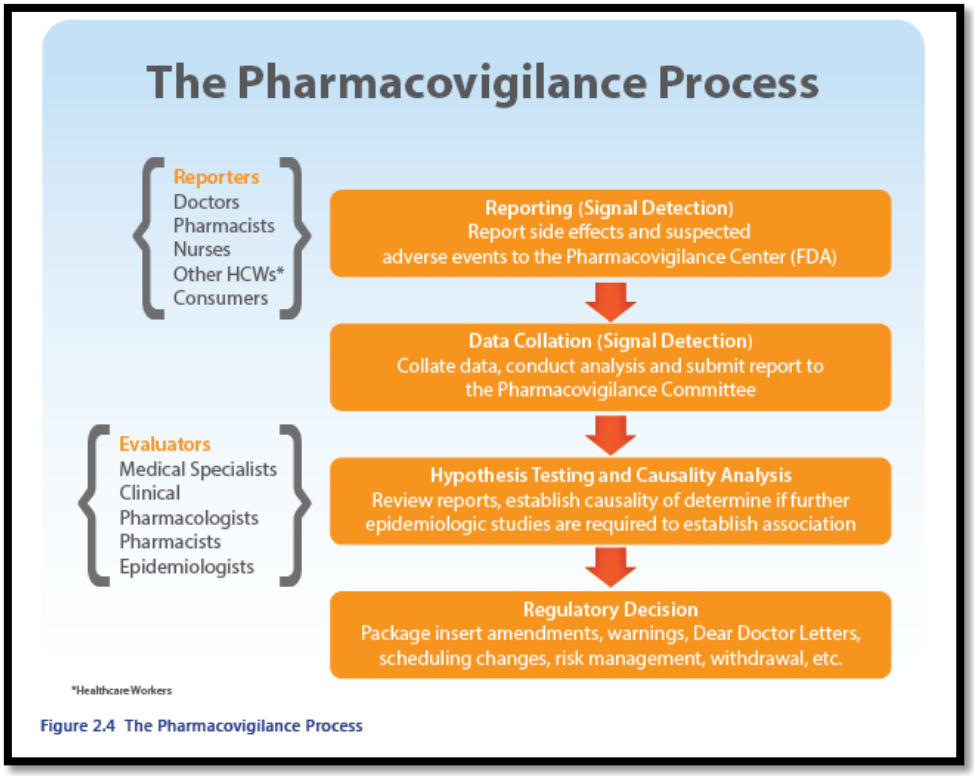

Fig no. 1: process flow of PV

Aims of pharmacovigilance

i. Improve patient care and safety in relation to the use of medicines and all medical and Para medical interventions.
ii. Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.
iii. Pharmacovigilance keeps track of any drastic effects of drugs.
iv. Improve public health and safety in relation to the use of medicines.
v. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
vi. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public [18]

"**Role of pharmacovigilance" in medicines regulation"**

Robust regulatory arrangements provide the foundation for a national method of medicine safety,

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and for public confidence in medicines. To be effective the remit of drug regulatory authorities needs to go further than the approval of new medicines, to encompass a wider range of issues relating to the safety of medicines, namely:

i. Clinical trials;
ii. The safety of complementary and traditional medicines, vaccines and biological medicines
iii. The development of lines of communication between all parties which have an interest in medicine safety, ensuring that they are able to function efficiently and ethically, particularly at times of crisis.
iv. In order to achieve their respective objectives pharmacovigilance programmes and drug regulatory authorities must be mutually supporting
v. On the one hand, pharmacovigilance programmes need to maintain strong links with the drug regulatory authorities to ensure that the latter are well briefed on safety issues in everyday clinical practice, whether these issues are relevant to future regulatory action or to concerns that emerge in the public domain. On the other, regulators need to understand the specialized and pivotal role that pharmacovigilance plays in ensuring the ongoing safety of medicinal products.

National pharmacovigilance centres are responsible for:

i. Promoting the reporting of adverse reactions;
ii. Collecting case reports of adverse reactions;
iii. Clinically evaluating case reports;
iv. Collating, analyzing and evaluating patterns of adverse reactions;
v. Distinguishing signals of adverse reactions from "noise";
vi. Recommending or taking regulatory action in response to endings supported by good evidence;
vii. Initiating studies to investigate significant suspect reactions;

➢ **What to report**

The National Pharmacovigilance Programme (NPP) shall encourage reporting of all suspected drug related adverse events, including those suspected to have been caused by herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions would be important since it may highlight a widespread prescribing problem.

The programme particularly solicits reports of:

- All adverse events suspected to have been caused by new drugs and 'Drugs of current interest' (List to be published by CDSCO from time to time)
- All suspected drug interactions
- Reactions to any other drugs which are suspected of significantly affecting a patient's management,
- including reactions suspected of causing:
- Death
- Life-threatening (real risk of dying)
- Hospitalisation (initial or prolonged)
- Disability (significant, persistent or permanent)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

➢ **Who can report?** Any health care professionals (Doctors including Dentists, Nurses, and Pharmacists) may report suspected adverse drug events. The Programme shall not accept reports from lay members of the public or anyone else who is not a health care professional.

➢ **Where to report?** After completion the form shall be returned/forwarded to the same pharmacovigilance Centre from where it was received. Reporting can be done to any one of the country vide pharmacovigilance Centres nearest to the reporter. (Complete list of pharmacovigilance Centres is available at www.cdsco.nic.in) In case of doubt the form may be sent to the national pharmacovigilance Centre at: Central Drugs Standard Control Organisation, New Delhi.[18]

➢ **Morbidity and Mortality of ADRs**

Adverse drug reactions are ranked as one of the top 10 causes of morbidity and mortality in the developed world ,Adverse drug reactions are documented in the USA to claim 100 000 to 218 000 lives annually and are the third leading cause of death after heart disease and cancer , However, the burden of the problem may actually be underestimated, as in many instances, ADRs are not suspected, thereby leading to under-reporting . Adverse drug reactions represent a vast economic burden in terms of healthcare costs, contribute to a significant percentage of hospital admissions and are regarded as a major public health problem . In the USA, the costs resulting from drug related problems in the ambulatory care setting were estimated to exceed US$177 billion annually.[1]

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Table 1. Activities currently included in the scope of pharmacovigilance

Category	Specific Activities/Functions	Phase(s)*
Supporting patient safety during the conduct of clinical trials	Informed consent, institutional review board, data monitoring committee	1-4
Selecting the first safe dose; first-in-human	Preclinical data, especially PK/PD parameters	1
Establishing the safety profile	Assessing all phases of development, focusing on dose limiting toxicity, maximum tolerated dose, AEs of special interest, on-target and off-target toxicities	1-4
Communicating information to stakeholders	Maintaining standard formats: Investigator's Brochure, Company Core Data Sheet, package insert, ClinicalTrials. gov	1-4
Attending to surveillance activities	Determining relationships between drugs and adverse events through passive and active method	1-4
Monitoring safety-related issues that involve the quality of the manufactured product	Conducting health hazard assessments for manufacturing deviations, complaints	1-4
Managing risk: REMS, RMP	Understanding benefit risk across patient populations and uses	1-4
Maintaining inspection readiness	Preparation for scheduled and unscheduled inspections of department activities	1-4
Training	Clinical investigators; internal customers throughout the company; vendors	1-4
Advertising and promotion review	Assuring consistency with important safety information	4

➢ **Pharmacovigilance of herbal medicine**

The safety of herbal medicines has become an issue for the regulatory authorities, as serious effects have been reported, including hepatotoxicity, renal failure and allergic reactions (Perharic et al., 1995; Nortier and Vanherweghem, 2007). The World Health Organisation, recognising the growing importance of the use of medicines worldwide developed guidelines for the monitoring of herbal safety within the existing pharmacovigilance framework [10]

➢ **Challenges of herbal pharmacovigilance**

Herbal medicines in Europe come from all traditions including Chinese, Indian, north and south American and African systems as well as that of European systems. This diversity adds to the challenges of herbal pharmacovigilance including basic questions such as defining the most appropriate herb naming system (botanical, common, pharmaceutical name or herbal drug name) and validation of the botanical identity of the herbal ingredients. These are not normally an issue with monitoring synthetic medicines. Some of these questions, such as naming issues or adulterations, do not fit easily into the existing systems of pharmacovigilance or the electronic data systems that were developed for pharmaceuticals.

➢ **Specific challenges**

Unlike synthetic medicines, herbal medicines are typically chemically rich and complex products and not isolated single compounds. A number of factors can influence the qualitative and quantitative chemical profile including:

a. Geographical origin – climate, soil, photoperiod.
b. Genotype.
c. Parts of the plant – leaves, stems, root, root bark, etc.
d. Harvesting time (year, season, time of day) and conditions.
e. Storage, processing, extraction.
f. Combinations of herbs and/or processing of the combined herbs as medicines [10]

➢ **Herbal medicines and dietary supplements**

The classification and regulation of herbal products may vary between different countries/jurisdictions. In the EU they are classified as herbal medicines (regulatory implications) with requirements for safety and quality standards. Some herbs may be supplied as food supplements. In the US, herbal products are classified as dietary supplements or botanicals, not medicines. Quality will vary although GMP requirements were issued by the FDA in 2007. Pharmacovigilance reporting is not compulsory for manufacturers. In contrast a food supplement cannot claim to treat or prevent disease or contain a pharmacologically active substance.

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This can be a complex area with the same herb being supplied as a herbal medicine but also as an ingredient in a dietary supplement. There are regulatory implications. In Europe, herbal medicines are registered under two directives, either 'well-established use' or 'traditional herbal medicinal products' both of which have significant requirements for quality (GMP) and safety (amongst others).

➢ **Nomenclature and what was used**

Adverse reaction reports, whether submitted to regulatory authorities or published in the medical literature, are meaningless if the medicinal herb(s) or ingredients in a product cannot be identified. Names for medicinal herbs include the Latin scientific name, the common or vernacular name, the pharmaceutical name or pharmacopeial name or the specific herbal drug names (as used in Traditional Chinese Medicine (TCM)). Herbal prescriptions, product packaging or labels may have one or more of these (occasionally no label) depending on source and regulatory status of the product. These have to be interpreted with care as even the scientific names may have synonyms.

- **Initiatives to address nomenclature and quality issues**

There is currently no single reference list of medicinal plants which presents an authoritative view on their current scientific name and linking all synonyms of those plants that are found in the literature. The only names that are standardised are Latin scientific names (e.g. Bupleurum Chinese DC.);their standardisation is achieved through the 'International Code of Nomenclature of algae, fungi, and plants' (ICN formerly ICBN). A new initiative, the Medicinal Plants Names Index (MPNI) underway at the Royal Botanic Gardens Kew will address this issue (http://www.kew.org/science-research-data/directory/ projects/MPNI.htm). Working with a wide range of stakeholders, one of this project's main aims is to develop an authoritative index to scientific plant names mapped to frequently used vernacular, trade and pharmacopoeia names in order to support the development of global, industry-wide medicinal data standards.

➢ **Source–users of herbal medicine**

Surveys have shown that consumers tend to self-prescribe herbal medicines without consulting a professional herbal practitioner or other health professional (Barnes et al., 1998; Ipsos Mori, 2008). Products can be bought over-the-counter from pharmacies, supermarkets, markets or the internet without any consultation with a health professional. Herbal medicines are prescribed by orthodox medical professionals in few European countries (e.g. Germany). Consumers may not be aware that adverse effects of herbal medicines can be reported to their general practitioner or know how to report to regulatory authorities. In addition, consumers may not associate the herbal product with the effect. A number of studies have shown that consumers are reluctant to admit to their physician that they have been using herbal medicines

➢ **Identifying adverse reactions**

The classification of types of adverse reactions is well established in orthodox medicine and applies equally to herbal medicine. Adverse reactions are classified as (Edwards and Aronson, 2000):

i. **Type A** (acute/augmented); dose related and explained by pharmacology of herbs.
ii. **Type B** (bizarre/idiosyncratic); not dose related or predictable by pharmacology.
iii. **Type C** (chronic/cumulative): cumulative effect.
iv. **Type D** (delayed onset) carcinogenic, genotoxic.

The safety of herbs is mostly based on empirical experience and is effective in identifying acute toxicity with a rapid onset of symptoms within hours or days of using any herbal medicines. However this traditional experience is not effective atidentifying herb(s)that cause cumulative, chronic or delayed toxicity. If the first signs of adverse effects are not recognised until months or years after starting or even stopping use of the herbs/drugs the use of the herbs is likely to be forgotten with such a delay[10]

➢ **Pharmacovigilance methods**

`A range of methods are used for post marketing monitoring of drug safety including **spontaneousreporting** and **prescriptioneventmonitoring** (Dyn Page UMC). These methods can be used for monitoring herbal safety but require modification to address specific challenges such as botanical nomenclature, quality, adulteration, labelling issues, prescriber/reporter differences and under-reporting

➢ **Monitoring for herb–drug interactions**

There is a perception that herbal medicines are safe, even if taken at the same time as prescription drugs (Delgoda et al., 2004). Herbs may be used to treat the primary condition or to reduce the side effects of their conventional treatment. Under-reporting of suspected interactions between herbs and drugs is of increasing concern and arises from the same reasons as under-reporting of herbal ADRs. The particular problems that need to be addressed are those that may affect specific patient groups where the

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incidence of combining orthodox and herbal medicine use is thought to be high, and the risk of interaction significant, such as in cancer patients. However any patients who are on drug regimens involving potent medicines metabolised by cytochrome P450 enzymes or where bioavailability is affected by P glycoprotein are at increased risk of experiencing herb–drug interactions.

➢ **Herbal practitioners**

Herbal practitioners are potentially a useful source of information on ADRs but with varying levels of professional regulation in Europe they are not necessarily recognised as ADR reporters. Some herbal practitioner organisations have established their own reporting schemes but these are not necessarily linked to official agencies. There are benefits to reporting by trained herbal practitioners. They are educated in the use of the medicinal herbs and should know actions and potential toxicity of the herb and be able to identify unexpected effects of the treatment. Herbal prescriptions are routinely modified to reduce side effects or improve responses. [10]s

➢ **The value of patient reporting to the pharmacovigilance system**

A total of thirty four studies were included. Five of the studies were reviews (two of which systematic reviews), fourteen retrospective observational studies, nine surveys and six applied mixed research methods. Patient reporting has the advantages of bringing novel information about ADRs. It provides a more detailed description of ADRs, and reports about different drugs and system organ classes when compared with HCP reporting. In addition, patients describe the severity and impact of ADRs on daily life, complementing information derived from HCPs. Patient reporting is relatively rare in most countries , Patient reporting adds new information, and perspective about ADRs in a way otherwise unavailable. This can contribute to better decision-making processes in regulatory activities. It identified gaps in knowledge that should be addressed to improve our understanding of the full potential and drawbacks of patient reporting.[7]

Table no. Evidence on the contribution of patients to pharmacovigilance through reporting ADRs to authorities [7]

Summarized evidence of the studies	Results and comments
Clinical evidence	-
1. Most frequently reported SOC	**a.** Nervous system disorders **b.** General disorders and administration site conditions **c.** Musculoskeletal and connective tissue disorders **d.** Psychiatric disorders **e.** Gastrointestinal disorders
2. Most frequently reported medicines	**a.** Pregabalin **b.** Simvastatin **c.** Sex hormones (drosperinoneand oestrogen) **d.** Serotonin-selective reuptakeinhibitors (duloxetine, citalopram) **e.** Influenza vaccines
3. Most frequently reported ADRs (PT level)	**a.** Nausea **b.** Headache **c.** Dizziness **d.** Somnolence **e.** Fatigue
4. Signal detection	**a.** Amenorrhoea, shock-like paraesthesia'sand micturition associated with serotoninselective reuptake inhibitors **b.** Weight loss, inflammation of the eye, change in sense of taste **c.** Pathological gambling associated with gabapentin **d.** Ear ache, thirst, stomach discomfort, associated with influenza vaccine **e.** Patchy baldness, dry skin, food allergy, associated with papillomavirus vaccine
5. Gender	Female reporters represent around 60% of all reports

Subjective evidence	-
1. Difference in reported information compared with HCPs	**a.** Patients report on impact of ADR on daily life **b.** Add more information on medication, personal characteristics
2. Seriousness	**a.** Patients report more disability than HCPs **b.** Definition of 'seriousness' might differ between patients and HCPs
3. Reasons to report	**a.** Altruism seems to be the main reason to report **b.** Wanting to have an independent voice fromHCPs seems important

Resources for pharmacovigilance centres
The following books shall be provided to various centres as identified by the NPAC: Current editions of:

i. Meyler's Side Effects
ii. AHFS Drug Information hand book
iii. Martindale/online
iv. Davies Text Book of ADR
v. Physician's Desk reference
vi. British National Formulary [18]

Conclusion: This is systematic review of studies evaluating PV performance and provides an in-depth understanding of factors of PV system .

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