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Pharmacovigilance – A Need for Best Patient Care in Pakistan. A review

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Abstract: The drug is unique commodity as being life saving and improves quality of life when used rationally, but it becomes life threatening when used irrationally/ inappropriately. Efficacy, safety and quality of the drugs are three most important characteristics in any registration criteria anywhere on the globe**.** However**,** pre registration research/studies on theses aspects can not be extrapolated to effectiveness of drugs under real user conditions. Drug related morbidity and mortality (DRMM) including adverse drug reaction (ADR) is a universal costly problem. The fast growing discipline Pharmacovigilance (PV) focuses on multiple activities which are specifically aimed to improve patient care, assessment of benefit /rationality/safety/effectiveness/risks notification in relation to drug therapy/ quality of medicines and prevention of ADR or any other drug-related problem (DRP). Pharmacovigilance is now at the top of health care all over globe but unfortunately it is practically non-existent in Pakistan. We desperately needs to design/develop and implement vibrant Pharmacovigilance system through collaborative efforts of academia, health care providers including pharmacist , patient ,manufacturer ,government , media , civil society, Uppsala Monitoring Center (UMC), Sweden operating under World Health Organization (WHO), FDA, ISoP. and other international organization working on drug safety. All concerned in drug delivery system must believe in the notion that disease related mortality is sometimes unavoidable but drug related death is now unacceptable. The costs of any ADR becomes high when trust of patients in the health care system is lost.Pakistan needs to think globally while acting locally while designing and implementing PV-programme for best patient care.Implementing concept of Pharmaceutical Care would give an in built Pharmacovigilance within health care system of Pakistan.Pharmacist should take PV as an opportunity for best patient care in Pakistan.

Key words:
Pharmacovigilance, DRMM, Drug related problems, ADR, Uppsala Monitoring Centre (UMC), World health organization (WHO), Pakistan

INTRODUCTION

The present review paper is presented with the basic aim to highlight the significance and need of "Pharmacovigilance "for ensuring best patient care in Pakistan.

Health is a fundamental human right recognized in Islam and all the civilized states practicing any religion or no religion. Access to health care, including effective and safe drug therapy, is central to this right. However, drugs are unique and different because of having multiple effects whenever these encounter any biological system. These are life saving when used appropriately/rationally but the same become dangerous/life threatening when used inappropriately. These effects are thus categorized as desired or undesired. Genetic and environmental factors contribute a lot toward variability in response to same drug therapy. Health care systems (including Pharmaceutical Sector) are now undergoing considerable evolutionary as well as revolutionary change all over the globe. The Pharmaceutical sector is continuously and persistently growing because of increasing demand as almost everyone needs/takes/receives some drugs at sometimes during his life. In spite of difficult market conditions and patent expiry of several blockbuster drugs, the global pharmaceutical markets expanded to $850 billion in 2010 and are expected to grow at 6% to reach US. $ 937 billion in 2012. Generic drugs constituted US$ 92 billion of global pharmaceutical sales and are expected to grow at 11% to reach US$ 155 billion in 2012. The value of pharmaceutical market within Pakistan in 2007 exceeded US$1.4bn, and is expected to exceed US$2.3 B by 2012[1-3]. This scenario demands immediate reshaping of drugs delivery system at national as well as at international level. One should always remember that quality of drug under many circumstances is questionable in many developing countries.

The pharmaceutical sector is highly regulated everywhere on the globe and every drug whether-it's prescription or over-the-counter must be approved by authorities after detailed evaluation and exhaustive scrutiny by professionals. The pre registration safety of a drug in is evaluated the by considering side effects, cGMP, animal testing and clinical trials (CT) etc. [4]. "Collet 2000 has reported the major limitation of randomized clinical trials which are their restriction to interventions that are

supposed to have a positive effect, difficulty to interpret or generalize the results because the studied population is very different from the population treated in normal life, the specificity of the questions answered; the narrow perspective leaves aside important information related to the consequences of the intervention on quality of life, inadequate quality control, sponsor interest, satisfaction or costs. Clinical trials usually do not provide the answers to the questions asked by practitioners and deciders". The Information regarding rare/serious adverse drug reactions (SADR's)/drug interactions/chronic toxicity and use in special populations (e.g. pregnant women, geriatrics and pediatrics). Thus effectiveness, tolerability and safety of drugs must be evaluated under real user condition. The evolution of surveillance from a role of controlling severe adverse reactions attributable to individual molecules to one of promoting a comprehensive assessment of the benefit/risk profile of drugs as they are utilized in society would definitely help and support many innocent, unaware, helpless patient and adversely suffering society. No drug is good or bad. It is manner of use which determine clinical good or adverse outcome such as cure of disease or adverse drugs reaction. William Withering. "Discoverer of Digitalis"1789 was right while stating that poisons in small doses are the best medicines; and useful medicines in too large doses are poisonous However, it is well settled universal truth that rational drug therapy targeted to achieve positive clinical outcomes requires knowledge, judgment, skill, wisdom, courage, empathy, responsibility and above all a sense of accountability for consequential best possible [5-11].

Perhaps the greatest of all drug disasters was the thalidomide tragedy of 1961-1962 when thalidomide caused major birth defects in an estimated 10 000 children in the countries in which it was widely used for the treatment of nausea and vomiting in early pregnancy. The WHO Programme for International Drug Monitoring (PIDM) was set up in 1968 as a consequence of the thalidomide tragedy. The rationale for setting up the WHO International Programme for Adverse Reaction Monitoring, 30 years ago was to make it possible to identify rare adverse drug reactions (ADRs) that could not be found through clinical trial programmes this incident became the modern starting point of a science focusing on patient problems caused by the use of medicines. This science and activities associated with it is now most commonly called pharmacovigilance. The intention of the WHO Programme was to ensure that early signs of previously unknown medicine-related safety problems would be identified and information shared by and acted upon throughout the world. Since 1978, responsibility for managing of the WHO-PIDM has been carried by the Uppsala Monitoring Centre (UMC) located in Sweden, It. It is a collaborating centre for maintaining global ADR database – Vigibase. WHO promotes PV at the country level with Collaboration of UMC? The ultimate purpose of UMCs work in pharmacovigilance is to support good decision-making regarding the benefits and risks of treatment options for patient taking medicines. As per Update on 4th August, 2011, the WHO Programme has 105 countries as official member and 35 countries (including Pakistan)) as associate member. In January 2009 the UMC published and circulated a short booklet for member countries describing the benefits and responsibilities of membership of the WHO Programme, entitled Being a Member of the WHO Programme for International Drug Monitoring [12-15]...

FDA from USA always led the world on the issue of Drug Safety and ADR surveillance / reporting. It is evident from the fact that FDA had started to collect reports of adverse drug reactions and to sponsor hospital drug monitoring systems in1960 well before thalidomide tragedy in 1961-1962,The FDA- Med-Wtatch of USA is still one of the best and most efficient and accessible resource The MedWatch July 2011 Safety Labeling Changes posting includes 32 products with safety labeling changes to the following sections: Boxed Warnings, Contraindications, Warnings, Precautions, Adverse Reactions, Patient Package Insert, And Medication Guide. The "Summary Page" provides a listing of drug names and safety labelling sections revised [16-17].

Globalization under WTO has changed world and also has a strong impact on of the pharmaceutical sector. It is bringing different challenges related drug safety. For example, prescription as well as non-prescription medicines are becoming increasingly available to the general public in all countries, including through such channels as the internet. Yet resources for monitoring their safety and quality are often lacking [18]. Thus there is need for calls for a better and more efficient level of international pharmacovigilance.

The discipline Pharmacovigilance based upon watchfulness in respect of danger; care; caution; circumspection related to drug use is well established in developed /advance countries ,

growing in some developing countries and practically non-existent in many countries including Pakistan.

PHARMACOVIGILANCE

The etymological roots are, Pharmacy – vigilance comes from Greek work Pharmakon means DrugLatin = Vigilare , "To keep awake or alert, to keep watch", "To keep watch on drugs, in particular their safety". Pharmacovigilance is defined by the WHO as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. PV is vital and applies throughout the life cycle of a medicine equally to the pre-approval stage as to the post-approval. [19-20]. Consequent upon continuous on-going activities on the issue of drug safety, Pharmacovigilance has emerged as new discipline. It is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of drugs or any other possible drug-related problem. [21-24].

As stated above, certain adverse drug reactions may not be detected until a very large number of people have received the medicine. Many drugs were withdrawn from the market after approval/ registration. These included thalidomide (1961, congenital limb defects), benoxaprofen (1982, hepatotoxicity), phenformin (1982, lactic acidosis),fenfluramine (1997, heart-valve abnormalities), astemizole (many drug interactions),phenylpropanolamine(2000,haemorragi c stroke), kava kava(liver abnormalities) cerivastatin (rhabdomyolysis).cisapride (cardiac arrhythmias),rofecoxib (2004, cardiovascular events), valdecoxib (2005, cardiovascular events, serious skin reactions),comfrey, senecio (nephrotoxicity),tegaserod (2007, cardiovascular events),clobutinol (2007, cardiac arrhythmia).Rofecoxib, a cyclo-oxygenase-2 selective inhibitor, marketed in 1999 and used by 2 million people in over 80 countries worldwide It was indicated for osteoarthritis and rheumatoid arthritis, and higher dose strengths were indicated for short term relief of acute pain (Vioxx Acute).However, in 2004, the pharmaceutical company Merck had initiated a voluntary immediate worldwide withdrawal of its bestselling arthritis drug rofecoxib (Vioxx), because new research shows that it almost doubles the risk of myocardial infarction and stroke if taken for 18 months or more. Pharmacovigilance is therefore one of the important post-marketing tools in ensuring the safety of pharmaceutical, herbals and related health products. Its role, need and scope are now widely reported and well documented. [25-30], the role can be divided into following areas:

1. To identify, quantify and document drug-related problems.
2. To contribute to reduce the risk of drug-related problems in healthcare systems.
3. To increase effectively communicate knowledge and understanding of factors and mechanisms which are responsible for drug-related injuries.
4. Assessment of drugs related risk / benefit ratio
5. The scope of pharmacovigilance continues to broaden as the array of medicinal products grows. The irrational drug use, overdoses polypharmacy and interactions, increasing use of traditional and herbal medicines with other medicines, illegal sale of medicines and drugs of abuse over the Internet, increasing self-medication practices, substandard medicines, medication errors and lack of efficacy are all within the domain of pharmacovigilance. Current systems need to evolve in order to address this broad scope adequately. Another aspect of broadened scope is the lack of clear boundaries between: Blood Products, Biological Medical Devices. Cosmetics, Food Additives Vaccines.

"Pharmacovigilance is needed for the prevention of drug-induced human sufferings and to avoid financial risks associated with unexpected adverse effects". Its major objectives are

I. To improve patient care and safety.
II. Ensuring public confidence by improving public health and safety.
III. To contribute to the assessment of benefit, harm, effectiveness and risk of medicines.
IV. Promoting rational use of medicines and adherence.
V. To promote understanding, education and clinical training for giving reasonable degree of freedom to use clinical judgement for drug therapy.
VI. To promote international co-ordination towards the highest ethical, professional and scientific standards in protecting and promoting safe use of medicines and in establishing a new culture of transparency, equity and accountability in communicating drug safety information

DRP, Pharmaceutical Care (PC) and PV.

Drug-related problems (DRP) is one of the central issues under globally fast growing practice of Pharmaceutical Care (PC) .The DRP is an integral

component within WHO definition of Pharmacovigilance.Thus, it is vital to understand and appreciate that PV is an integral part within PC which is directly related to patient centred – outcome oriented pharmacy practice ensuring effective and safe drug therapy. The point is explained below in the light of literature [31-36]

Pharmaceutical care is defined as the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. These outcomes are

- Cure of a disease;
- Elimination or reduction of a patient's symptomatology;
- Arresting or slowing of a disease process; or
- Preventing a disease or symptomatology.

Pharmaceutical care involves the process through which a pharmacist cooperates with a patient and other professionals in designing, implementing, and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient. This in turn involves three major functions:

- Identifying potential and actual drug-related problems;
- Resolving actual drug-related problems; and
- Preventing drug-related problems.

Pharmaceutical cares practitioners are co-ordinate with other health care provide to ensure that drug-related problems are identified, resolved and prevented that therapeutic goals are achieved. Therapeutic relationship is mandatory to meet drugs-related needs of patient. Pharmaceutical care is now becoming a necessary element of health care system all over the globe and should be integrated with other elements. Pharmaceutical care is, however, provided for the direct benefit of the patient, and the pharmacist is responsible directly to the patient for the quality of that care. The fundamental relationship in pharmaceutical care is a mutually beneficial exchange in which the patient grants authority to the provider, and the provider gives competence and commitment (accept responsibility) to the patient. The fundamental goals, processes, and relationships of pharmaceutical care exist regardless of practice setting.

Since the concept of Pharmaceutical Care was introduced from United States about twenty years ago, this initiative has become a dominant form of practice for thousands of pharmacists around the world. Currently, pharmaceutical care is understood as the pharmacists' compromise to obtain the maximum benefit from the pharmacological treatments of the patients, being therefore responsible of monitoring their pharmacotherapy. As the profession has moved from a product orientation (dispensing medications) to a patient focus, clinical training requirements have expanded. This is a slow but on-going process, which started from a philosophical point of view, in order to transform the concept of Pharmacy from commodity-based, mercantile operations into a clinical profession in the community pharmacies. According to a 1994 study, the provision of pharmaceutical care has the potential to save between $30.1 - $136.8 billion to the health care system, mostly due to fewer drug-related hospitalizations.

Drug-related problems (DRP) used synonymously with Drug therapy problems are undesirable events or risks experienced by the patient that involve or are suspected to involve drug therapy and that inhibit or delay him/her from achieving the desired goals of therapy. These problems are identified during the assessment process, so that they can be resolved through individualized changes in the patient's drug therapy regimens. The following are Categories of Drug Therapy Problems. [37-39]

1. **Unnecessary drug therapy**. The drug therapy is unnecessary because the patient does not have a clinical indication at this time
2. Needs additional drug therapy. Additional drug therapy is required to treat or prevent a medical condition.
3. **Ineffective drug**. The drug product is not effective at producing the desired response
4. **Dosage too low**. The dosage is too low to produce the desired response
5. Adverse drug reaction. The drug is causing an adverse reaction
6. Dosage too high. The dosage is too high resulting in undesirable effects
7. **Noncompliance.** The patient is not able or willing to take the drug regimen appropriately.

Controlled studies have also been carried out to determine the impact of pharmaceutical care as delivered by community pharmacists These studies were conducted in developed countries and established the clinical, economic and humanistic viability of pharmaceutical care Pharmaceutical care practitioners are co-ordinate with other health care provide to ensure that drug-related problems are identified, resolved and prevented that therapeutic goals are achieved. Therapeutic relationship is mandatory to meet drugs-related needs of patient. (40-41)

Adverse Drug Reaction under Pharmacovigilance:

Adverse drug reactions (ADRs) are common, often unrecognised and typically under-reported However, update knowledge and skills related to detection, assessment, prevention, management and transparent notification / reporting of ADR is essential for an efficient **Pharmacovigilance everywhere on the globe.** Some definitions related to PV are given below. [42-50]

Definitions Related To ADR

ADR is defined as any response to a drug that is noxious and unintended and that occurs in man at doses for prophylaxis, diagnosis, or therapy, including: new, rare, or previously poorly documented reactions.

1) ADRs associated with newly marketed medications
2) Serious, life-threatening, or fatal reactions.
3) According to the Food and Drug Administration, a serious adverse event is one in which the patient outcome is death, life-threatening), disability, hospitalization (initial or prolonged), a congenital anomaly, or necessitates medical or surgical intervention to prevent permanent impairment or damage.
4) Unusual increases in numbers or severity of reactions.
5) Allergic reactions and idiosyncratic reactions are also considered ADRs, if they are deemed to be serious, life threatening, or fatal, as described above.

However, the definition of ADR shall not include:

a) Adverse effects of the drug which are related to the size of the dose, expected, well-known reactions and do not result in changing the care of the patient...
b) Drug withdrawal, drug-abuse syndromes, accidental poisoning, and drug-overdose complications (e.g., drowsiness from diphenhydramine).
c) Reactions which are extensions of the pharmacologic effect for which the drug is given (e.g., bone marrow suppression with antineoplastic agents).
d) Disturbances totally dependent on the pathological state (e.g., diarrhoea from cancer and not from a laxative).

Adverse effect. This term encompasses all unwanted effects; it makes no assumptions about mechanisms, evokes no ambiguity and avoids the risk of misclassification the terms “adverse reaction” and “adverse effect” are interchangeable, except that an adverse effect is noted from the point of view of the drug; an adverse reaction is observed from the viewpoint of the patient.

Adverse Event (AE) Any adverse occurrence in the health of a clinical trial participant who is administered a drug, device or research intervention that may or may not be caused by the administration of the drug, device or research intervention.

Serious Adverse Event (SAE) An adverse drug reaction or adverse event that: Results in death or is life threatening or requires in-patient hospitalization or prolongation of existing hospitalization or Results in persistent or significant disability or incapacity, or Causes congenital malformation.

Unexpected Serious Adverse Drug Reaction A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator’s brochure or on the label of the drug.

Expected Adverse Reaction An adverse reaction identified in regulatory documents such as the Investigators Brochure or Product Monograph occurring within the expected frequency estimate; or identified in the Research Ethics Board (REB) submission and letter of information to participants; or is related to study intervention and was the result of the natural progression of the person’s disease/illness and/or state of health.

Related to the Drug or Research Intervention: There is a reasonable possibility that the reaction or event may have been caused by the drug or research intervention (i.e. a causal relationship between the reaction and the drug or research intervention cannot be ruled out by the investigator).

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction that is both serious and unexpected (i.e. the nature and severity of which is not consistent with the information about the IMP in question set out in the Summary of Product Characteristics (SmPC) for that product and/or in the Investigator's Brochure or study protocol

Drug safety: Absence of ADRs and freedom from unintended, unwanted negative or excessive effects of drugs

Classification of Adverse Drug Reactions

The following classification introduced by Rawlin & Thompson in1991. Is the most frequently and commonly used [51]

1. Dose related or Augmented. Common related to pharmacological action of drug, predictable .e.g., haemorrhage seen with warfarin. Respiratory depression with opiates, bradycardia with beta blockers and hypotension with antihypertensive.
2. Non dose related or Bizarre Uncommon, unpredictable, not related to pharmacological action of the drug e.g.; phocomelia with thalidomide tragedy which revolutionized the monitoring to ensure safe and effective use of medicine ,cv effects with cox-2 inhibitors, vaginal cancer in young women with stilbestrol penicillin hypersensivity, malignant hyperthermia
3. Dose & time related or Chronic Uncommon, related to cumulative dose e.g.; HPA axis suppression by corticosteroids, Benzodiazepine dependence
4. Time-related or Delayed Uncommon, usually dose related. Delayed onset e.g.; teratogens, carcinogenesis, tardive dyskinesia
5. Withdrawal or End of use Uncommon. Occurs soon after drug is stopped e.g.; opiate withdrawal syndrome
6. Unexpected failure of therapy or **Failure** Common, dose-related, often caused by interactions with other drugs e.g.; Decreased oral contraceptive effectiveness when used with anti-tuberculosis medication.

Ferner and Aronson have proposed a comprehensive mechanistic classification of adverse drug effects in 2010. This classification called as EIDOS is based upon five elements which are , the Extrinsic chemical species (E) that initiates the effect; the Intrinsic chemical species (I) that it affects; the Distribution (D) of these species in the body; the (physiological or pathological) Outcome (O); and the Sequela (S), which is the adverse effect. This classification EIDOS, describes the mechanism by which an adverse effect occurs; it complements the DoTS classification of adverse effects (based on clinical pharmacology), which takes into account Dose responsiveness, Time course, and Susceptibility factors. Together, these two classification systems, mechanistic and clinical, comprehensively delineate all the important aspects of adverse drug reactions; they should contribute to areas such as drug development and regulation, pharmacovigilance, monitoring therapy, and the prevention, diagnosis, and treatment of adverse drug effects[52].

Cost of ADR

The high cost associated with ADR is widely and continuously reported in literature Morbidity and mortality from drug-induced diseases has of late been recognized as an important item on the public health agenda in developed and developing countries. ADRs are the 4^{th}-6^{th} largest cause for mortality in the USA. ADRs account for approximately 10% of hospital admissions Norway 11.5%, France 13.0% UK 16.0%[2] The Institute of Medicine[2] reported that in the US More than 100,000 deaths may occur yearly due to ADRs The cost of preventable ADEs. Approximately $2.8 million yearly for a 700-bed teaching hospital. This is the equivalent to salary of 35 full-time pharmacists and $2 billion for the nation. ADRs increase the length of hospital stay and medical costs. 15-20% of hospital budget may be spent dealing with drug complications verified that the ADR are among leading cause of admission to hospital. In our study the mean hospitalisation length of the surveyed psychiatric patient population was compared to that of the serious ADR cases. The length of hospitalisation for serious ADR cases showed to be more than doubled. The costs of treatment of ADR are increasing. The work on the subject has also been done in the neighbouring country India. Retrospective analysis of reports submitted to FDA Adverse Event Reporting System during 1993 and 1998 clearly indicated that mortalities associated with ADE due to medication errors had raised. Authors of a meta-analysis estimated that ADRs alone—excluding medication errors—killed over 100,000 people in 1994 and were the fourth to sixth leading cause of death in the United States **[53-59].**The cost of ADR becomes more painful when one consider that about 30-80% of ADRs may be preventable. A UK based study estimated that over 70 percent of ADRs that resulted in hospitalization were preventable [60-64].

Understanding ADR-Causality Is Vital For PV.

Every occasion when a patient is exposed to a new medicinal product is a unique situation and we can never be certain about what might happen. However we can learn from previous experience when patients under similar conditions have been exposed to the same or similar medicine. The healthcare professional may be uncertain that the drug caused the ADR Uncertainty about the causality between a suspected ADR and the drug used is mentioned by both physicians and pharmacists as a barrier to the submission of reports. This is perhaps unsurprising, and signifies a scientific way of thinking that

requires certainty for action. However, it is unfortunate that this mind-set prevents some from reporting. After all, pharmacovigilance concerns the gathering of data on suspected ADRs. It is the task of the national reporting centres to establish the causality between reported suspected ADRs and the drugs used by elimination of as many uncertainties as possible by means of causality assessment and statistical methods [65].

Understanding ADR-Causality is of great significance for any efficient PV-programme anywhere. Some definitions and explanations are given below. Relationship between drug and an adverse event may be graded as follows: **[66-68].**It is the probability that an ADR is due to a drug and refers to individual cases and the assessment of what a healthcare professional would call clinical likelihood that the ADR was due to the drug. The relationship of an AE to the study drug is graded as follows:

(a) **None:** The AE is definitely not associated with the study drug administered.
(b) **Remote:** The temporal association is such that the study drug is not likely to have had an association with the observed event.
(c) **Possible:** This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) could have been produced by the participant's clinical state or other modes of therapy administered to the participant.
(d) **Probable:** This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) abates upon discontinuation of the study drug; (iii) cannot be reasonably explained by known characteristics of the participant's clinical state.The essential distinctions between 'Probable' and 'Possible' are that in the latter case there may be another equally likely explanation for the event and/or there is no information or uncertainty with regard to what has happened after stopping.
(e) **Definitely related:** This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) abates upon discontinuation of the study drug; and (iii) is confirmed by reappearance of the adverse event on repeat exposure (re-challenge).

WHO-UMC Causality Categories are **Certain (**Event definitive**), Probable/ Likely (**Unlikely to be attributed to disease or other drugs**), Possible (**Could also be explained by disease or other drugs**), Unlikely (**relationship improbable but not impossible)**, Conditional/Unclassified (**More data for proper assessment needed**)** and Unassessable/Unclassifiable **(**Data cannot be supplemented or verified**) [69].**

The US Food and Drug Administration (FDA) has released its latest list of drugs to monitor based on potential signs of serious risks or new safety information identified in the agency's Adverse Event Reporting System (AERS).The quarterly watch list released on February 8, 2011, consists of 13 drugs that treat a wide range of conditions, including cough, angina, diabetes, cancer, and bipolar disorder. The FDA is studying the 13 drugs to determine whether they are causally linked to the possible risks reported through AERS from July to September 30, 2010. The drugs are considered pharmacologically innocent until proven guilty. According to the FDA physicians should not stop prescribing these drugs, nor should patients stop taking them. Among the 13 drugs are Lithium citrate (Eskalith), Lopinavir/Ritonavir oral solution (Kaletra) & Pioglitazone HCl (Actos). According to the article, Lopinavir/Ritonavir has been associated with serious adverse events in neonates, Pioglitazone with rhabdomyolysis & Lithium citrate with Brugada syndrome (a hereditary syndrome that causes sudden unexpected cardiac death in apparently healthy young males) [70].

ADR-REPORTING

An efficient ADR reporting system is vital for any Pharmacovigilance programme anywhere on the globe. It is explained below after perusal of reported work on the subject [71-79].

It is now an accepted, understood routine and integral to the healthcare professionals' duties in many developed countries like USA, Europe, Canada and Japan. Every single ADR case report is important and can make a major difference. For example, the case report on thalidomide causing phocomelia by the Australian obstetrician had created a huge awareness among the drug regulatory authorities and healthcare professionals worldwide. The worldwide withdrawal of block buster NSAIDs rofecoxib, in 2004 is asking redefining of drug safety monitoring. WHO Database includes around 4.6 million reports (January 2009), [6] growing annually by about 250,000.Many developing countries worldwide either have very poor or have no ADR reporting system. FDA had started to collect reports of adverse drug reactions and to sponsor hospital drug monitoring systems in1960

well before thalidomide tragedy in 1961-1962.But unfortunately, Pakistan is among the countries having practically no monitoring system for drug safety. However, some fast growing countries like Malaysia and India have taken up the challenge of ADR notification and reporting. Even some African countries like Nigeria and least developed country Nepal are also making extra ordinary effort to develop Pharmacovigilance programme suited to their local condition. The following are the most common types of ADR reporting

1. Spontaneous adverse drug reactions (ADR) reporting
2. Voluntary adverse drug reactions (ADR) reporting
3. Mandatory adverse drug reactions (ADR) reporting

Post-marketing surveillance is essential to decides whether the benefits of a drug outweigh its risks. All the above reporting programs have been made integral part of regulatory as well as drug use process in health care systems of developed countries. Spontaneous adverse drug reactions (ADR) reporting is considered the cornerstone of any pharmacovigilance system. Although many countries have made ADR reporting as part of application for registration of drugs but with some exception, the post marketing surveillance is not vibrant. FDA-USA has the best in built system for mandatory adverse drug reactions (ADR) reporting. The user friendly ADR- reporting systems are available at the websites of UMC_WHO, , ISoP , FDA- MedWatch of USA, and Yellow Card Scheme of UK .The herbal preparations and unlicensed medicines found in cosmetic treatments are now included in ADR- reporting systems. Guidelines prescribed under this system for submitting adverse event reports should be followed for ensuring quality reports.

The evidence indicates that patient reporting of suspected ADRs has more potential benefits than drawbacks. Evaluation of patient reporting systems is needed to provide further evidence.A quantitative and qualitative analysis on patients' and health professionals' reports of ADRs to statins was done in Netherland following telecast of TV programmes related to awareness of risk and benefits of statin. Results indicated that media attention affects drug use and ADR reporting by patients. Patient reports can provide additional information, making them a useful source of information next to health professional reports. [80-84]

Non Reporting & under Reporting of ADR is the single big issues having negative impact on PV anywhere on the globe. Many studies have given different reasons for none, under and poor reporting, complacency and uncertainty about the medicine causing the reaction, poor adverse reaction reporting protocol and indifference. The common contributory factors and reasons reported are [85-89].

1. Lack of time
2. Lack of Knowledge and Skills about ADR
3. Complacency and Uncertainty about adverse drug reaction – causality
4. Complex ADR reporting form
5. Ignorance About Pharmacovigilance
6. Lack of knowledge on what, how or where to report
7. The reaction is already well known
8. Guilt or fear of litigation
9. Belief that all medicines are safe
10. Reputation

Many ADR reporting program mainly targets physicians who are not welcoming to report at the cost time reserved for medical practice. It has been reported that physicians fail to report ADRs for several reasons and neither financial incentives nor compulsory legislation seems to be the solution. However, in an attempt to increase reporting many countries allowed hospital pharmacists, community pharmacists, nurses and even patients to report ADR.

SIGNAL DETECTION

The WHO definition of pharmacovigilance signal is ‘reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously”. Signal detection is one of the most important objectives of pharmacovigilance; the whole process risk/benefit evaluation depends on effective detection of signals. Classical signal detection is driven by incidence counts of AEs and is retrospective and not truly predictive. The vision is to utilize the vast sets of medical data to proactively identify and manage emerging safety signals. Automated signal generation based upon comparison with reported safety profile of other products is an emerging method for signal detection. Proportional Reporting Ratio, Bayesian Combination Propagation Neural Network is used by the WHO Uppsala Monitoring Centre and the Modified Gamma Poisson Shrinker method is used by FDA. Automated systems facilitate spontaneous reporting, which is the core of pharmacovigilance by creating better signal detection standards, helping with earlier

detection and analysis of signals, and offering tremendous savings in terms of money, time, and manpower [90-93].

EU-ADR consortium had carried a study by analysis of electronic health record databases for signal detection in pharmacovigilance. An initial list comprising 23 adverse events was identified. After rating all the events and calculation of overall scores, a ranked list was established. The top-ranking events were: cutaneous bullous eruptions, acute renal failure, anaphylactic shock, acute myocardial infarction, and rhabdomyolysis [94].

The detection of quality and appropriate signals needs rational clinical assessment aided by statistical and epidemiological analysis. The efficient and easy notification based pharmacovigilance models are vital for detection and generation. Many countries have efficient safety alert system swiftly informing and updating all concerned about safety and risks and of medicines. Some examples from FDA, USA are reproduced below. [95]

The FDA warned health-care professionals & patients that there is an increased risk of myopathy in patients taking the highest approved 80 mg dose of simvastatin compared to patients taking lower doses of simvastatin & possibly other statins. The most serious form of myopathy is rhabdomyolysis, a rare adverse event reported with all statins. The risk of myopathy is increased when simvastatin, especially @ higher doses, is used with certain drugs. The FDA recommends that Itraconazole, Ketoconazole, Erythromycin, Clarithromycin, Telithromycin, HIV protease inhibitors & Nefazodone are not used with simvastatin due to potential drug-drug interactions. They also recommended that - Gemfibrozil, Cyclosporine, Danazol - not be used with more than 10mg of Simvastatin. Amiodarone & Verapamil must not be used with more than 20mg of Simvastatin. Diltiazem should not be used with more than 40mg of Simvastatin.

February 8, 2011 — The US Food and Drug Administration (FDA) has released its latest list of drugs to monitor based on potential signs of serious risks or new safety information identified in the agency's Adverse Event Reporting System (AERS).The quarterly watch list consists of 13 drugs that treat a wide range of conditions, including cough, angina, diabetes, cancer, and bipolar disorder. The FDA is studying the 13 drugs to determine whether they are causally linked to the possible risks reported through AERS from July to September 30, 2010. The drugs are considered pharmacologically innocent until proven guilty. According to the FDA physicians should not stop prescribing these drugs, nor should patients stop taking them. Among the 13 drugs are Lithium citrate (Eskalith), Lopinavir/Ritonavir oral solution (Kaletra) & Pioglitazone HCl (Actos). According to the article, Lopinavir/Ritonavir has been associated with serious adverse events in neonates, Pioglitazone with rhabdomyolysis & Lithium citrate with Brugada syndrome (a hereditary syndrome that causes sudden unexpected cardiac death in apparently healthy young males). For more information go to http://www.medscape.com

COMMUNICATING DRUG SAFETY INFORMATION AND PHARMACOVIGILANCE

Every occasion when a patient is exposed to a new medicinal product is a unique and different situation. One can never be certain about what might happen following administration of drug. However we can learn from previous adverse experience when patients under similar conditions have been exposed to the same or similar medicine. The honest transparent communication of ADR is vital for any PV programme everywhere. ADRs can be reported by a number of healthcare professionals including doctors, pharmacists and nurses, as well as patients.

It must be appreciated and acknowledged that flaws and short comings in drug safety communication within any health care system lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored. Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust. The following statements set forth the basic requirements for this to happen, and were agreed upon by all participants from 34 countries at Erice: Transparent and credible monitoring, evaluation and communication of ADR and drug safety based upon high scientific/ethical/professional standards are vital for any good PP. The Erice Declarations Of 1997 and subsequent Erice Statement Of 2009 provide very good foundation in this regard. The Erice Declaration on Communicating Drug Safety

Information, first published in September 1997, provided a vision of vigorous, open, ethical, patient-centred communications in drug safety that the world has yet to achieve. Drug safety information must serve the health of the public through ethical and effective communication in terms of both content and method. [96-98]

The Use of the Internet is becoming widespread throughout the world. Its use in the domain of drug safety and pharmacovigilance is spreading rapidly. Governments and industry have taken the lead in developing extensive web sites. The US Food and Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA) and other agencies have developed sites containing enormous amounts of information both on pharmacovigilance in general and on specific drugs in particular. Under the US 'Freedom of Information Act' the FDA has put major parts of its adverse event database on line. Regulatory documents are also available from the FDA site or from hyperlinks described in the site. The US Centre for Drug Evaluation and Research updates its site most days and maintains a free automated e-mail announcement service of these updates. Similarly, the EMEA updates its site frequently and publishes extensive material including regulatory documents, guidelines, European Public Assessment Reports on newly approved medications and other useful information. A free update service by e-mail is also available. Pharmaceutical companies are not using the Internet for Pharmacovigilance yet. Rather, the Internet is being used for promotion of their products and for informing consumers on general information on diseases, for financial and investor data and for employment opportunities, etc. Other organisations such as lobbies, consumer groups and medical journals are also beginning to use the Internet. The electronic transmission of safety information, using the standards developed by the International Conference on Harmonization, is currently being tested for the transmission of individual patient adverse event information between companies and governments. In addition, the FDA has begun to accept adverse events from healthcare providers and consumers directly on line using an electronic version of its MedWatch form. It is expected that these developments will change the nature of the way pharmacovigilance is carried out. Significant issues will arise from this including privacy concerns. The European Union's 1995 directive on 'the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC)' went into effect in October 1998. The enabling legislation now being passed by the member states will produce significant changes in the way companies and governments handle individual patient data in order to assure the privacy and protection of individuals. The user comments to health related social networks do contain extractable information relevant to pharmacovigilance. This approach has the ability to detect novel relationships between drugs and adverse reactions. [99-103]

Pharmacogenetic and Pharmacovigilance

ADR confirmation may require supportive Pharmacogenetic studies may be required either to re-challenge or de-challege. Which are presently not carried out or are lacking [104].

Pharmacovigilance and Environment

Around the world, thousands of tons of pharmacologically active substances are used annually but surprisingly little is known about the ultimate fate of most drugs after their intended use. A large proportion of an administered dose (up to 90%) may be excreted, unchanged, while metabolites can be converted back to the active compound via bacterial action. Despite receiving attention and necessary action by regulatory agencies like FDA and the European Union, there is a lack of substantial procedures regarding impending monitoring of drug concentrations in the environment and the palpable adverse effects. In 2006 a new concept entitled as 'Pharmacoenvironmentology' was suggested as speciality of PV by Syed Ziaur Rahman Pharmacoenvironmentology is a branch of pharmacology and a form of pharmacovigilance concerning entry of chemicals or drugs into the environment after elimination from humans and animals. It may be an extension of Pharmacovigilance dealing specifically with the effects pertaining to the environment and ecology of drugs given in therapeutic concentrations. Pharmacologists having this particular expertise (pharmacoenvironmentologist) may be made a compulsory component of the team assessing different aspects of drug safety. The corresponding author for this review paper differ from Syed Ziaur Rahman on the point that Pharmacoenvironmentology is a part of pharmacology. In his opinion the subject should come under the discipline Pharmacy and it should be Pharmenvironmentology instead Pharmacoenvironmentology. Monitoring the effects of drugs /pharmaceutical products on environment is

vital safeguard of ecosystem as well as ultimate public health[**105-107**],

Pharmacovigilance and Alternate System of Medicines The use of natural product to counter human suffering is probably as ancient as the human being himself. This commonly known as Alternative medicine that is a group of diverse medical and health care systems, practices, and products that are not presently considered as the same class as evidence based standard medicine. The safety of herbal medicines has become a major concern to both national health authorities and the general public. The use of herbs in Traditional medicines continues to expand rapidly across the world. Many people now take herbal medicines or herbal products for their health care in different national health-care settings. However, mass media reports of adverse events tend to be sensational and give a negative impression regarding the use of Herbal medicines in general rather than identifying the causes of these events, which may relate to a variety of issues. That is important to educate people to use OM appropriately to make harmony with modern medicine. European Union legislation for traditional herbal medicinal products will require manufacturers of products registered under new national schemes to comply with regulatory provisions on pharmacovigilance. In the longer term, other improvements in safety monitoring of herbal medicines may include modifications to existing methodology, patient reporting and greater consideration of pharmacogenetics and pharmacogenomics in optimising the safety of herbal medicines. [108-113]

PHARMACIST AND PHARMACOVIGILANCE

The reasonable and unbiased fair professional used to say that Pharmacists are over trained for what they do and underutilized in what they know. The evidence base research in Pharmacy has clearly shown that status and respect of pharmacist has raised parallel to increase in clinical role within hospital. [113-114].

Pharmacists have traditionally been involved in the preparation and dispensing of medications, at the direction of the physician. But, with the shift in the model of pharmacy from a focus on the medication to a focus on the patient, there is need for a shift in the pharmacist's approach as well. This shift can be described as moving from the health professional–centered "MEDICAL MODEL" to the patient –centered "HELPING MODEL. Pharmacist of today work as a Health Care Professional/ Provider who is patient–oriented with a unique body of knowledge and skills to contribute in our health–care system. This new breed of pharmacist is more clinically and patient–oriented and better prepared to dispenses the appropriate drug product but also has the knowledge to assure safe and rational use of drugs. There is need for professionals who are patient–oriented and able to apply and provide drug knowledge to improve drug use in the health care system. [115-116].

Literature is flooded with evidence base reports(117-129) indicating either direct or indirect role and association of Pharmacist with pharmacovigilance.

Community Pharmacists are the most accessible HCP for the patients all over the globe. Different studies have been carried out with the aims to investigate the knowledge, perceptions and practice of Pharmacovigilance amongst community pharmacists in different countries including in Malaysia, Nigeria, India, Norway, Holland, USA, and China. Result indicated that majority of pharmacist believed that the role of the pharmacists in ADR reporting was important. The community pharmacists had positive attitude and were willing to practice pharmacovigilance if they were trained... The pharmacists were confused about ADR reporting and had very little knowledge about it in developing and least developed countries.

Pharmacists are uniquely positioned to play a role in Pharmacovigilance which is an important component in any quality pharmacy services anywhere on the globe... Evidence has shown that' pharmacists deliver best drug therapy through pharmaceutical care and consequently, have positively contributed in better patient care by ensuring effective and safe use of drugs.

ADR reporting is at the heart of any Pharmacovigilance anywhere all over the globes. Studies in various countries have examined the level of pharmacists' attitude to ADR reporting Factors cited by the surveyed pharmacists as deterrents for reporting ADR include, pharmacists were unsure that the drug caused the reaction, unavailability of reporting forms, pharmacists did not know how to report an ADR, the ADR is expected, pharmacists did not think of reporting the ADR and fear of legal liability. The participation of the pharmacist in national spontaneous reporting systems for adverse drug reactions (ADRs) has not always been a matter of course. Even today, there are a number of countries, in particular the Scandinavian countries, where pharmacists are not authorized to report

ADRs. In those countries in which they are allowed to report, they do not always use this opportunity.

A comprehensive review of the literature was done in order to investigate the involvement of pharmacists in ADR reporting. In addition, evaluation of the pharmacists' actual contributions was done in 2001 by means of an international questionnaire-based survey among the countries participating in the WHO Drug Monitoring Programme in September 2002. Apart from the numbers of pharmacists' reports, respondents were asked to indicate their assessment of both the quality and the significance of the contribution. Of the 68 participating countries, 41 responded by returning the questionnaire. The appreciation of pharmacists' ADR reports was high in those countries that have more experience with greater numbers of pharmacists' reports. If the specific contribution pharmacists can make to the quantity and quality of ADR reports were to be exploited to a greater extent, this could lead to a substantial improvement in international adverse drug reactions reporting.

Intensive monitoring can be a valuable tool in the early detection of adverse drug reactions, especially of new drugs. Study in USA has concluded that pharmacists and prescribing physicians are able and willing to contribute to an intensive monitoring system for new drug..

An investigation showed that hospital pharmacists in a northern region of China had a reasonable knowledge of and positive attitudes towards pharmacovigilance. However, the majority of pharmacists had never reported an ADR in their career. Pharmacists' ADR education and increasing involvement in patient care would be important in improving ADR reporting in hospitals .

Pharmacy students undertaking internship in a community pharmacy willingly participated in a project specially designed to explore their role in ADR reporting. Hundred and twenty eight ibuprofen users participated in the study out of who thirty three reported forty five ADRs possibly linked to ibuprofen use. The reported ADRs followed earlier reported patterns of distribution with gastric pain showing up as the most commonly reported symptom followed by heartburn, nausea, diarrhoea and constipation. It was concluded that through adequate training community pharmacy internship students get competencies and are capable of detecting and reporting ADRs through direct questions to drug users..

The educational programme clarified their role and increased their knowledge about the reporting requirements There is an urgent need for international as well as national support for starting educational programs to train pharmacists about pharmacovigilance and ADR reporting in all those countries who have realised the significance of pharmacovigilance for the best patient care and safety.

PHARMACOVIGILANCE IN PAKISTAN:(130-136)

Islamic Republic of Pakistan with a Population: of 184.7 million is an important player on the globe. In Pakistan, a National Health Policy (NHP) exists. In 2001, it was updated. [125].Health is the fundamental human right and access to essential medicines/technologies as part of the fulfilment of the right to health, is recognized in the constitution or national legislation.

Pakistan has a very vibrant and forward looking Pharma Industry. At the time of independence in 1947, there was hardly any pharma industry in the country. Today Pakistan has about 500 plus pharmaceutical manufacturing units including those operated by 25 multinationals present in the country. The Pakistan Pharmaceutical Industry meets around 70% of the country's demand of Finished Medicine. The domestic pharma market, in term of share market is almost evenly divided between the Nationals and the Multinationals. The value of pharmaceuticals sold in 2007 exceeded US$1.4bn, which equates to per capita consumption of less than US$ 10 per year and value of medicines sold is expected to exceed US$2.3 B by 2012.

National Drug Policy of Pakistan was notified in 1997 as an integral component of its National Health Policy, purpose of which was to ensure regular availability of essential drugs of acceptable efficacy, safety and quality at affordable prices to all irrespective of their socio-economic status or place of living. Pakistan has a drug legislation, a quality control system, and certain other elements of a drug policy in fragmented form, but to meet the

challenges of the day, a more comprehensive drug policy is necessary.

Pakistan has very good infrastructure for patient care but unfortunately will and implementation is not there. due many vested interst. The high number of non qualified and unscientific healer (Quacks) are among major contributors toward irrational drug therapy in Pakistan.

The implementation of NDP remained very poor.It is interesting pharmacovigilance was not present in this policy.There is neither any system nor any organization related to pharmacovigilance which is fast growing concept and process vital for delievery of safe and effective drug therapy.The corresponding author is supervising a research project on Pharmacovigilance to evaluate awareness and knowledge of health care providers(HCP) on this subject.Results have shown that more than 95% HCP were totally unaware on this important concept.

In Pakistan, there are legal provisions requiring the Marketing Authorization holder to continuously monitor the safety of their products and report to the MRA. Laws about monitoring Adverse Drug Reactions (ADR) exist in Pakistan. A national Pharmacovigilance centre linked to the MRA does not exist in Pakistan. An official standardized form (available at website of MOH) for reporting ADRs is used in Pakistan [14]. A national ADR database does not exist in Pakistan. In the past 2 years, no ADR reports are sent to the WHO database in Uppsala. ADRs are not monitored in public health programs (example TB, HIV/AIDS).

For pharmacovigilance networks to be at their most effective, they must be harmonised to internationally recognised standards. Individual Case Safety Reports (ICSRs) are of great significance. ICSRs in old WHO format have been converted to the international ICH-E2B format as well as extended interpretation of the ‘world wide unique id’ on ICH-E2B cases. The reason behind the harmonization is to facilitate both the handling and interpretation of case safety data in VigiBase. The harmonization process also detected around 4,000 duplicate cases in VigiBase and these were ‘history marked’ during the summer of 2009.Today world is a global village and Pakistani pharmacovigilence system must be harmonised. In its comprehensive report on the Importance of Pharmacovigilance, released in 2007, the WHO said since the late 1990s steps have been taken to harmonise standards at regional and inter-regional levels. "The driving force of these efforts was the increase of global trade in pharmaceutical products and the growth in complexity of technical regulations related to drug safety and quality," it noted.The report went on to say "there needs to be better consultation and communication between developed and developing countries when discussions on international harmonization of pharmacovigilance issues are taking place.

Some other issues of relevance to pharmacovigilance include substandard medicines, irrational drug use, overdoses, medication errors, lack of efficacy reports, increasing self-medication practices, increasing use of traditional and herbal medicines with other medicines, illegal sale of medicines, use of medicines for indications that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, assessment of drug-related mortality, abuse and misuse of medicines, polypharmacy and adverse interactions of medicines with chemicals, other medicines, and food.

The pharmacist in Pakistan must understand and accept challenges related to patient care in new era in new millennium. Every pharmacist must be responsible and accountable as now pharmacy services are evaluated on patient outcome rather than the number of prescriptions dispensed as pharmacist has now trained toward interpretation and patient consultation, related to the effective and safe use of drug. The pharmacist therefore must learn to view medication’s use from the patient’s perspective and his primary concern is the of Life / welfare of humanity / the relief of human suffering. The Pharmacovigilance should be taken as challenge as well as opportunity by the Pharmacists in Pakistan as making it as an integral part of Pharmacy practice will ensure delivery of best possible drug therapy for the ultimate benefit for patient. Furthermore, effective and efficient participation of pharmacist in PV will bring lot of respect and honour for Pharmacy profession in Pakistan.

The community pharmacist in Pakistan may help many patients by very simple and free of cost interventions . Simple advice that take analgesics and NSAIDs before or after food will minimize ADRs related to NSAIDs.

The policy maker in Pakistan may get benefits and guidance from the European Medicines Agency 'Road map to 2015'which sets out the Agency's vision in further developing its role as a European public-health agency in the field of medicines and has been drafted in consultation with the Agency's partners and stakeholders to ensure as broad a consensus as possible on the best way forward. The road map proposes three priority areas for future

actions to strengthen the Agency's role in protecting and promoting human and animal health in the European Union:

1. Addressing public-health needs by: stimulating medicines development in areas of unmet medical needs, neglected diseases and rare diseases, and for all types of medicines for veterinary use; facilitating new approaches to medicines development; applying a more proactive approach to public-health threats where medicines are implicated.
2. Facilitating access to medicines by: addressing the high attrition rate during the medicines-development process; reinforcing the benefit/risk-balance assessment model; continuing to improve the quality and the regulatory and scientific consistency of the outcome of the scientific review.
3. Optimising the safe and rational use of medicines by: strengthening the evidence base in the post-authorisation phase to enable better regulatory decision-making; enhancing patient safety by avoiding unnecessary risks to patients as a result of the use of medicines; becoming a reference point for information on medicines evaluated by the Agency; improving the decision-making process by taking due account of patient experience, thus contributing to the rational use of medicines.

RECOMMENDATIONS

1. The new Multi-professional Patient Safety Curriculum Guide has been released by WHO in October 2011 which promotes the need for patient safety education to improve the safety of care. The comprehensive guide assists universities and schools in the fields of dentistry, medicine, midwifery, nursing and pharmacy to teach patient safety. It also supports the training of all health-care professionals on a number of priority patient safety concepts to improve learning about patient safety.The capacity building may become easy by adopting these guidelines in Pakistan.
2. The Pakistan Pharmacovigilance Advisory Council should be constituted through legislative and revolutionary restructurings of the existing dormant pharmacovigilance system in Pakistan. This PV system connected to UMC_WHO, FDA and ISoP should full fill need to explore, develop and fund new PV-activities so that safety data sources available in many different countries can be used effectively. Furthermore, ADR data based on the Pakistani population must be generated within built mechanism for automatic sharing of the information with global health-care community through WHO-UMC. Council must give a vision capable of transforming to reality.Pakistan need to focus on the quote “Think Globally Act Locally “
3. Establishment of national pharmacovigilance systems (NPS) for the reporting of adverse events, including national, regional and ditiirct pharmacovigilance centres. The official website links to several email subscription services and acessable for health care providers ,must be developed.It must integrated with international data.. Patient and anyone concerned with drug safety. Development of legislation/regulation for medicine monitoring under PV sytems is vital . Maintain contacts with international regulatory bodies working in pharmacovigilance and exchange information on drug safety would be of great benefits.
4. The operational pharmacovigilance systems connected to NPS must be developed at all primary, secondary and tertiary health care fascilities.Reporting and documentation must be simple and easy for all.
5. The culture of ADE notification must be developed in Pakistan. Healthcare providers need to be motivated by their professional conscience to comply with ADR-reporting requirements. Conceptual framework and operational approach to strengthen pharmacovigilance systems will be key to success.
6. Pakistan needs to develop Good Pharmacovigilance Practice comparable to international standards.
7. Promote understanding, education and clinical training in pharmacovigilance.
8. The effective / transparent PV.communication to the entire health care provider and the public is vital .Follow up and feed back always bring excellent result as for as trust and understanding are concerned.
9. Media must be engaged to promote risk benefits of drugs. However, programs and articles must be within the frame work of law. The risk of harm is less when medicines are used by an informed health profession and by patients who themselves understand and share responsibility for their drugs...
10. Effective safety surveillance, improved support for decision-making by regulators on safety

issues and ultimately reduction in risk to patients. An efficient mechanism to translate pharmacovigilance knowledge into clinical practice must be developed in order to achieve safer drug therapy.

11. FDA Guidance for Industry for Good Pharmacovigilance Practices and Pharmacoepidemiologic may be taken as frame work for development of Good Pharmacovigilance Practices for Pharmaceutical Industry of Pakistan for safety signal identification as well as interpretation and pharmacovigilance plan development.
12. Pharmaceutical industry of Pakistan should aggressively take up the challenge to start research in Pharmacovigilance by collaboration with Universities. One of the reasons for the western world's dominance in R&D is due to the strong research collaboration that exists between the universities and the industry. This is very much vital and essential for a country like Pakistan which is now spending lot of money in higher education / research and opening up... Government must fascinate and contribute to this activity.
13. These should include hard end-points indicating the impact on mortality and morbidity. Surrogates, such as the impact on prescribing of medicines, are more readily available and are also potentially valuable, Systematic audit of pharmacovigilence processes and outcomes should be developed and implemented based on agreed standards ('good pharmacovigilence practice) and pharmacovigilence should operate in the culture of scientific development
14. Formulate National policy development (to include costing, budgeting and financing).continuing education of health-care providers on safe and effective pharmacotherapy.
15. Integration with WHO and other international initiatives (sharing best practices and resources) and local requirements to be included
16. WHO- UMC ,FDA and ISoP should be approached for Support/ visits to development of National , Provincial , District Pharmacovigilance Centers .The collaboration between the UMC and the Department of Toxicology, University of Uppsala,provided a five-week undergraduate course on drug safety and pharmacovigilance to pharmacy students in November 2008 and again in February 2009. Pakistan may approach WHO-UMC for the benefits of Pharmacist in Pakistan for such traning.
17. Public awareness program regarding benefit of Pharmacovigilance should be a continuous on going process.
18. Government must legislate (including PV) to regulate manufacturing under Alternate System of Medicines.The menace of quackery under the cover of this system must be eliminated as it the source for imbalncse between risks and benefits of medicines and adversely affect drug safety.

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