



# Drug Safety Surveillance: Modern Trends and Industrial Action

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## ABSTRACT

The primary aim of patient care is to provide the best medication that can produce the best treatment with minimal or no harm. This is only possible when the entire health care workers play their card well through correct prescription, dispensing, drug administration and adequate patient monitoring. However, the outcome is not always favorable because of the limited time undergone by the drug during premarketing studies as well as the bias by the pharmaceutical-industries to get approval from regulatory-agencies. As a result of this many safety data and information are lacking. Therefore, in order to preserve patient confidence and integrity of pharmaceutical products, post-marketing surveillance has become necessary. The methods commonly used in post-marketing surveillance include spontaneous reporting, data mining and active reporting which have meaningfully contributed to patient safety. Despite the improvement made, spontaneous reporting have some disadvantages such as underreporting, poor quality of reports, and cannot be used to determine risk rate. Pharmaceutical companies as owners of the drug have noteworthy role to play in adverse drug reactions monitoring and can adopt similar techniques used by the regulatory-agencies and academic research. Unfortunately, this has led to reporting bias. This has suggested the need for more awareness and educational intervention for health care professionals at all levels. The curriculum of training medical and health related students should be incorporated with PV programme. This appraisal has described how to identify adverse drug reactions and methods used in reporting, current developments in pharmacovigilance and role of pharmaceutical-industries in drug safety studies.

**Key words:** Patient-safety, Pharmacovigilance, Pharmaceutical-industries, Spontaneous-Reporting.

## INTRODUCTION

Post-marketing surveillance is an obligatory process to combat Adverse Drug Reactions (ADRs) after a new-drug is released for consumption. All drugs used in clinical practice have passed through preclinical and clinical trials in order to obtain data and information on their safety and efficacy using small sample of volunteer. Unfortunately, before drug is marketed all necessary data regarding ADRs cannot be obtained at satisfactory level.<sup>1-3</sup> This is because the duration of the study was short; the

Access this article online	
Journal Sponsor	Website: www.jyoungpharm.org
	DOI: 10.5530/jyp.2015.2.3

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nature of patients were different; the disease treated was not the same; when compared to use after approval and once more the majority of testing were conducted in animal-models which cannot guarantee human-safety.<sup>1,4</sup> In addition, information is lacking on drug-interactions, chronic-toxicity studies as well as use in neonates, pregnant and lactating women, geriatric patients, and patient with kidney or heart failure.<sup>2</sup> Therefore, in order to detect exceptional and unforeseen ADRs and ensure patient safety post-marketing surveillance has become indispensable. Research reported that only 6-10% of the ADRs detected are reported to the authorities.<sup>5</sup> Similar study also revealed that the rate of underreporting of ADRs was 94%.<sup>6</sup> Pharmacovigilance (PV) study is designed to protect the society from the atrocities of pharmaceutical products. It was established that 57% of drugs banned in India was due to cardiovascular delinquent, and 14% was as a result of liver-damage.<sup>17</sup> Worldwide, patient experiences ADRs which lead to increase morbidity, mortality and also hospitalization.<sup>17</sup> Meanwhile, ADRs is considered as global challenges prolonging patient hospitalization, increase workload of health care workers and health-care cost.<sup>8</sup> Study carried out in USA by institute of medicine account that, ADRs increase the cost of health care between 17 to 29 billion US \$ annually.<sup>8</sup> It was established that hospitalized patient who have been treated with 16 different medication have 40% chance of developing adverse drug events (ADEs). Similarly, patient that have experienced ADRs 2-3 times before are more likely to develop ADRs again.<sup>9</sup> An epidemiological study reported that 5% of all hospitals admission is due to ADRs which are always promotes treatment-failure.<sup>10</sup> Majority of these ADRs are considered as preventable. Henceforth, careful documentation and examination of patient history will help to avoid such threat.<sup>8</sup>

Spontaneous reporting (SR) is the commonest method used worldwide in detection, documentation and reporting ADRs.<sup>6,11,12</sup> In countries like Italy, Sweden and France ADRs reporting was made compulsory to all health care professionals.<sup>6</sup> In addition, USA have recently recognizes ADRs reporting by patient.<sup>6</sup> During post-marketing surveillance it is necessary to consider presence of medication error, side-effects and exacerbation of underlying disease which lead to ADEs. This is referred as 'noise' not real ADRs.<sup>6,13</sup> Information generated on ADRs during post-marketing surveillance need to be disseminated to all health care workers both in the hospitals and community settings even if the basis is not yet proven.<sup>14</sup> Hospital administration and also every individual health care professional are responsible to document ADRs and report to national Pharmacovigilance (PV) centre

for advance evaluation.<sup>12,14</sup> Subsequently, the national PV centers forward this information to the world Collaborating Centre for International Drug Monitoring (The Uppsala Monitoring Centre) which is responsible for assessing of all the reported ADRs and taking appropriate regulatory-action.<sup>14</sup> The main aims of this study are to describe how to identify ADRs and methods used in reporting, current developments in PV and role of pharmaceutical-industries in drug safety studies.

### Definition of Terms

- *Pharmacovigilance* is defined by WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.<sup>15,16</sup>
- *Adverse drug reactions* can be described as a response to a drug which is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.<sup>15,17</sup> However, the word "noxious" means injurious, hurtful, or harmful; this definition may include all kind of ADRs both major and minor.<sup>11,14</sup>
- *Adverse drug events* are 'any untoward medical occurrences that may present during the treatment with a medicine but does not necessarily have causal relationship with this treatment'.<sup>11</sup> Adverse drug event refers to any adverse outcome that happened during the treatment but not necessarily caused by the drug itself.<sup>15</sup>
- *Medication errors* are described as mistakes that occur during manufacturing, compounding, prescribing, dispensing or administration of medicine and related products which has potential to harm the patient.<sup>11, 13, 15</sup> Medication errors (MEs) can occur during any of the routine treatment stages from diagnoses up to the time the patient was discharged; therefore, it is important to identify the root cause of MEs in order to prevent it.

## HISTORY OF PHARMACOVIGILANCE

PV program was initiated in 1961 after the case report by Australian doctor on serious ADRs by drug thalidomide used as anti-emetic and sedative in pregnant women.<sup>2, 11,12, 18</sup> Subsequently, in 1968 WHO have strengthen the program on international drug monitoring with aim of collecting worldwide ADRs data at a central point. ADRs signals detected from all part of the world are received and document as individual case safety report (ICSR).<sup>2,12</sup> This is done through WHO global ICSR database system called VigiBase™. The global center of ADRs monitoring

is located in Uppsala, Sweden and by the April, 2013 this center have generated more than 8 million ADRs reports worldwide.<sup>2</sup> The term PV was coined by French group of pharmacologist and toxicologist in 1970s which implied strategy promoting detection and assessment of side effects and ADRs.<sup>2</sup>

## MODERN TRENDS

### **Aims of pharmacovigilance**

The primary aim of PV is to detect early signals and try to establish causal relationship between the detected signals and the suspected drug by collecting similar information from different sources which involves observational and experimental studies.<sup>11,19</sup> It also involves monitoring the use of herbals products; traditional and complementary medicines; blood products; biological and medical devices; as well as vaccines.<sup>11,20,21</sup> PV is also aimed to detect substandard medicines; medication errors; use of medicines for indications that are not approved and inadequate scientific basis; acute and chronic poisoning; assessment of drug-related mortality; abuse and misuse of medicines; as well as adverse interactions.<sup>13,22</sup>

### **Specific objectives of pharmacovigilance**

The primary objectives of PV study are to improve patient care and safety.<sup>11,22</sup> Also to contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and cost-effective use; and to promote understanding, education and clinical training in PV and its effective communication to the public.<sup>23,24</sup>

### **How to identify ADRs**

Health care professional can identify ADRs by observing the patient and asking series of questions.<sup>25</sup> This will prevent prescription cascade that may lead to poly-pharmacy. Once ADRs is detected by health care professional or reported by patient, its causal relationship should be assessed immediately. Anaphylaxis usually occur in few minutes but a times it may take hours, days or month before it appears; in few case it may be observed in off spring.<sup>25</sup> ADRs that are dose-related may be identified by reducing the dose of medication and observed for reduction or fading of the reactions. Re-challenge may be appropriate to observe the possibility of reoccurrence especially if the patient is likely to benefit from the study.<sup>25</sup> Type-A reaction is easy to recognize because is an extension of drug pharmacological action. However, type-B reaction can only be identified if there were previous reports.<sup>25</sup> It is important to note that certain reactions are directly associated with ADRs

e.g. toxic epidermal necrosis, Stevens-Johnson syndrome, acute dystonia, blood dyscrasia and neuroleptic malignant syndrome.<sup>25</sup>

ADRs can also be detected through chart review which is more efficient in detecting ADRs than SR.<sup>8</sup> This involves the use of trigger tools to detect ADRs in a hospital setting. The idea was first introduced by Classen and his colleagues in 1991. They use computer and patients' medical record to track the possibility of ADRs.<sup>8</sup> Trigger is referred to any clue during review of patient medical charts that lead to further investigation which result in detection of ADE. Common triggers considered in identifying the possibility of ADRs include presence of antidote to any medication; drug withdrawal; patients' complains; medication records; laboratory results; nursing flow and physician progress reports.<sup>8</sup>

### **Yellow Card Scheme**

Yellow card scheme serve as an early warning and have been used to detect ADRs as soon as possible.<sup>25</sup> It provides valuable information on the type and nature of ADRs detected; nature and location of patient; and causal relationship.<sup>25</sup> The use of yellow card was introduced in 1964 after the thalidomide disaster. Initially only doctors were allowed to report but now pharmacist and nurse's correspondingly.<sup>25</sup> The PV process involves use of all data available on that drug from case report, epidemiological studies, and premarketing safety data.<sup>25</sup> However, recently there is substantial reduction in reporting ADRs which raises urgent awareness programme on ADRs reporting among all stakeholders. In UK yellow card can be forwarded directly to PV center via [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or [www.yellowcardwales.org](http://www.yellowcardwales.org); alternatively yellow card can be submitted to [www.bnf.org](http://www.bnf.org) or directly to the website of UMC.<sup>25</sup>

### **Assessment of ADRs**

ADRs reports may contain all the necessary details or incomplete without causality assessment and possible laboratory investigations.<sup>2,26</sup> Once the reports using yellow card is received by hospital based PV center, the causal relationship and possible risk factors determined. Then forward to regional PV center; it will be re-assessed then forward to national PV center which finally forward the report to WHO PV center in Uppsala Sweden.<sup>25</sup> Each report is vital even incomplete, can act as supportive evidence.<sup>26</sup> Subsequently, these reports will be subjected to hypothesis testing with aim of acquiring more information.<sup>2</sup>

## PRE-MARKETING SAFETY STUDY IN PHARMACEUTICAL-INDUSTRIES

### Preclinical Trials

The first step used in safety studies about a drug is preclinical trials. Drug manufacturers usually conduct preclinical trials to determine whether the drug has merit or not.<sup>27</sup> It involves in-vitro and in-vivo testing to determine the drug efficacy, toxicity, and pharmacokinetics profiles.<sup>27</sup>

### Clinical trials

Safety monitoring during clinical trials involves many stages including laboratory investigations, clinical examination of subjects, and ADRs monitoring.

#### Phase 0

This is called first-in-human trials. It was introduced recently for early decision making; and involves giving sub-therapeutic dose of a drug to small-number of volunteers.<sup>28</sup> Micro-dose was given to 10-15 subjects and quickly determines whether the drug has action in human or not.<sup>28</sup>

#### Phase I

This phase is conducted to confirm the safety and tolerability of the drug in humans. It takes usually 6 to 9 months.<sup>29</sup> The subjects involve are 20-100 healthy volunteers given single doses of drug and observed.<sup>29</sup> Testing includes observation, pharmacokinetics and pharmacodynamics evaluation. The pharmacokinetics is determined by taking blood sample and other body fluids.<sup>30</sup> If the drug under investigation is expected to have serious toxicity as in cancer and HIV agents, volunteer patients are used instead of healthy subjects.<sup>27</sup>

#### Phase II

Is designed to prove that the new drug has effective therapeutic activity; tolerated for long term use; and to determine most appropriate dose for human.<sup>27</sup> This phase of drug development generally takes 6 months to 3 years.<sup>27</sup> This phase is designed either as case series or randomized controlled trials with a placebo, a standard drug and the new drug groups. The drug is tested using up usually 100-500 patients with the disease of interest.<sup>27</sup> This testing is to determine safety and effectiveness of the drug. Also establishes the possible mechanism of action, minimum and maximum effective dose. However, phase-I and phase-II clinical studies refer to early clinical drug development.<sup>27</sup>

### Phase III

This study involves determination of efficacy and is often double blind randomized controlled trials.<sup>27</sup> It is also conducted with large number of volunteer patients (1,000-5,000) to generate statistically significant data about safety, efficacy and the benefit-risk relationship.<sup>31</sup> This phase usually requires 1-4 years. It is very expensive and time consuming because it determines the actual drug response.<sup>31</sup> Immunologic and genetically related effects of the drug may be revealed at this time. The studies also provide the information for labeling instructions. Once the drug proves to be satisfactory, a comprehensive data should be compiled and forward to regulatory-authorities for marketing approval.<sup>31</sup> This stage is considered to be the most demanding methodology to determining whether a relationship exists between a treatment and an outcome. However, this stage does not ensure the best practice to monitor the drug-safety.<sup>31</sup> It is generally not possible to identify ADRs that occur only rarely because of the limited number of patients. Another limitation of clinical trials is that the characteristics of the participants do not always correspond to the characteristics of the population in which it will later be used. Consequently, it is difficult to extrapolate the results obtained from clinical trials to the population at large.<sup>32</sup> In order to study rare ADRs and ADRs with a long latency careful monitoring of the drug in the post-marketing phase is obligatory.<sup>32</sup>

## POST-MARKETING SURVEILLANCE

The aims of PV within the industry are for all intents and purposes the same as those of regulatory-agencies. The two types of post-marketing studies are descriptive and analytical.<sup>32</sup> Descriptive study is carried out to generate ADRs signals (hypotheses) while analytical study is done to test hypotheses and determine associations or causal relations.<sup>32</sup> Descriptive studies are Spontaneous Reporting (SR) and Intensive Monitoring (IM) while analytical studies include case-control studies, cohort studies and post-marketing clinical trials.<sup>32</sup>

### Descriptive studies

*Spontaneous reporting* begins in 1961 following the report by Dr WG McBride published in Lancet. Pregnant women taking thalidomide deliver babies with congenital abnormalities like phocomelia.<sup>32</sup> The purpose of SR is the early detection of signals of new, rare and serious ADRs during diagnosis, treatment and post-medication.<sup>32</sup> SR involves determination of causal relation.<sup>26</sup> Causality and certainty about ADRs depend on the skills and

experiences of the health care professional.<sup>26</sup> The work of PV center is to gather and analyze the reports and inform stakeholders of the potential risk of new ADRs.<sup>32</sup> Despite the advantages of SR it suffers serious setback due to underreporting, unidentified reactions and false causality. Therefore medical doctors' professional responsibilities are jeopardized.<sup>33-37</sup> However, some doctors were able to report ADRs with certainty because the procedure is similar to routine diagnosis.<sup>26</sup>

### ***Intensive monitoring (active surveillance)***

Intensive Medicines Monitoring Program was introduced in the late 1970s and early 1980s in the UK and New Zealand.<sup>32</sup> This type of surveillance involves the use of data from previous prescriptions to identify ADRs. In addition, the prescriber will be asked about any ADRs happening following the use of the drug under-study.<sup>32</sup> All the information collected from the patient record will be assessed for the possibility of new ADRs signals. The concept of intensive monitoring is a non-interventional observational cohort studies which distinguishes it from SR because it only monitors selected drugs.<sup>32</sup> Similarly, intensive monitoring provides real world clinical data and enables the incidence of ADRs to be estimated.<sup>32</sup>

### ***Hypothesis testing (Analytical studies)***

After receiving adequate information on serious ADRs signals the next step is hypothesis testing to enable confirmation of causal association with the drug. Various methods used in hypothesis testing include case-control studies, cohort studies and post-marketing clinical trials.<sup>38</sup>

#### **• *Published case reports***

Health care professionals document some ADRs signals as case report and forward to regulatory-authorities. Several people were alerted on the possible drug hazard through publishing case reports.<sup>38</sup> However, the major disadvantage is that sometimes the reports contain incomplete information. Also subjected to editorial selection where personal liking always work, and there is substantial delay.<sup>38,39</sup> Adequate data and information on harmful drug through case report is advantageous because several report on similar incidence may serve as a caution. Published case reports are used by regulatory-authorities and drug-industries to get information about new ADRs signals by carrying out standard searches through databases.<sup>38</sup> In order to ensure safety, it has become necessary for the concern authorities to monitor any report arising from use a particular drug. However, standard post-marketing safety study is considered more important than case report

in generating new ADRs signal; although, case report is considered supportive evidence.<sup>38</sup>

#### **• *Cohort studies***

It is carried out after marketing the drug to generate hypothesis or answer safety question. It can also be used after signal detection to test for hypothesis. Cohort studies are conducted to monitor occurrence of ADRs in a particular group of patient and are designed as prospective, non-interventional.<sup>38</sup> It serves as an experimental study to confirm the previous case report of ADRs. This type of study may not be effective in detecting new ADRs signals due to long time taken to recruit the subject and usually no control groups.<sup>38</sup> Cohort study is difficult to carry out compared to other method of hypothesis testing. The study is also affected by restricted sample size, and majority of information obtained were considered as noise.<sup>38</sup>

#### **• *Post-marketing clinical trials***

Post-marketing clinical trials is conducted to provide more data and information on safety and efficacy of the drug. Using this method a lot of details will be obtained on the drugs that were not available from premarketing studies. Study involves large number of randomized patients subjected to different kind of treatment to avoid some of the problems associated with cohort studies.<sup>38</sup> The population of patients used is sufficient enough to provide more information. It may be long and expensive procedure. Hence it should be made as simple as possible.<sup>38</sup>

#### **• *Epidemiological studies***

This type of study is carried out to monitor the effects of drugs in large populations. Meanwhile, for the past few decades pharmacoepidemiology has significantly contributed to the knowledge and understanding of drug safety.<sup>38</sup> It was used to assess the relation between NSAID drug intake and occurrence of gastrointestinal ulceration and bleeding.<sup>38,40</sup> In addition, experts in pharmacoepidemiology are employed by drug-companies and regulatory-authorities to study many ADRs signals and drug-safety.<sup>38</sup> Similarly, many academic institutions are involved in pharmacoepidemiology research which is largely based on observation.<sup>38</sup> Despite the significant contribution made by this type of study, it suffers many setbacks such as methodological problems, confounding and bias.<sup>38</sup> This limitation is explained in the studies involving the 3<sup>rd</sup> generation oral contraceptives; some differences identified between classes of this drug were alleged to be as a result of confounding or bias or both rather than the real pharmacological differences.<sup>38</sup> PV

study is a very wide discipline with continuous evolution of ideas on daily basis; this work covered only the most relevant areas within the time limit.

## CONCLUSION

SR of ADRs is a multi-disciplinary procedure that requires careful detection, assessment and documentation. Several methods of detection, identification and documentation of ADRs were discussed which if properly studied by health care professionals and accurately implemented, significant improvement will be achieved. Substantial advancements have been made in the field of PV using SR technique and it has contributed a lot in drug safety and efficacy. Health care professionals must play a major role in reducing the hazard due to ADRs. However, according to the various research conducted knowledge, attitude and practice of health care professionals were generally poor. This has suggested the need for more awareness and educational intervention for health care professionals at all levels. The curriculum

of training medical and health related students should be incorporated with PV programme. Prescription, dispensing and administration of drugs are not the only challenges in health care delivery services in these days when new drugs are flooded in almost all countries. Therefore monitoring the ADRs caused by these drugs evolved as part of new concern. Drug regulatory-authorities, pharmaceutical-companies, healthcare professionals and academia must be proactive in ADRs detection, documentation and reporting

## ACKNOWLEDGEMENT

Authors are much grateful to the authority of UniSZA for kind cooperation.

## CONFLICT OF INTEREST

The research obtained no funding. The authors have no conflict of interest

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