Review Article

Starting-Up A Pharmacovigilance Network from Scratch: A Brief Plan

***Partha S. Saha**

Department of Biomedical Sciences, Faculty of Medicine, University of Leuven (KU Leuven), Leuven, Belgium.

ABSTRACT

Before releasing a drug in market, international drug regulatory agencies follow a common system to assess the safety and efficacy of a drug through preclinical and clinical trials. However, these pre-market evaluations are regarded as incomplete, which is the reason why post-market surveillances are constantly conducted to monitor the safety aspects of drugs as well as to detect adverse drug events. Pharmacovigilance (PV) is primarily concerned with the identification of adverse drug reactions (ADRs) and reduction of the associated risks. The detection of ADRs mainly depends on spontaneous reporting, stimulated post-marketing surveillance, and case-control studies. Detecting and reporting ADRs can make the trend of prescribing of medicines much safer and realize its aims. These are only possible if the pharmaceutical companies and patients from different places of a particular region report regularly on their adverse drug reactions. A PV network can harness these data by a systematic fashion from different levels of a social health care environment. Building-up an effective network calls for synchronization of different criteria, which again requires a perfect plan to set-up from early on. Basic steps in setting up a PV network include: creating guidelines, setting up of PV centers and capacitating its performance, data acquisition through ADR reporting form, creating public awareness for ADR reporting, detecting signals on an adverse drug events, and keeping connected with higher authorities. This article shortly reviews on these essentials, which a robust PV system demands for.

Keywords: Capacity building for PV network, medication errors, pharmacovigilance network, reporting of ADRs, signal detection

Received 19 Oct 2013 Received in revised form 01 Nov 2013 Accepted 06 Nov 2013

***Address for correspondence:**
Partha S. Saha
Department of Biomedical Sciences, Faculty of Medicine, University of Leuven (KU Leuven), Leuven, Belgium.
E-mail: p.s.saha.11@aberdeen.ac.uk

PHARMACOVIGILANCE

Pharmacovigilance (PV) system monitors the safe and effective use of drugs and other pharmaceutical medications. According to the definition of World Health Organization (WHO), pharmacovigilance is a "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" [1].

An organized PV system includes all resources that protect general people from medicine related adverse drug effects (ADEs). An organized PV system can protect the public health by efficiently identifying, collecting, and assessing of ADRs, and also by communicating those risks. And again those risks, in turn, support decision making to minimize risk at different levels of social health care environment.

Though all the ADEs suffered by patients after taking the medicines are not caused due to the medicine alone, they may occur due to patients' level of illness. When adverse clinical events of medicines are concerned, it may be due to poor quality of the drug, medication errors, unknown or known pharmacological properties of the administered drugs (**fig. 1**). ADEs are only preventable when they are caused due to medication errors [2].

Therefore, it is important to document the ADEs and adverse drug reactions (ADRs). This is very important for a new drug or a new pharmaceutical product. This guides to set a change if any measures are required to

recall the product from market or to change the dose level, packaging and labelling information and treatment guidelines. These identification and documentation of the ADRs and ADEs help to prevent the harm caused by them to the public health [2].

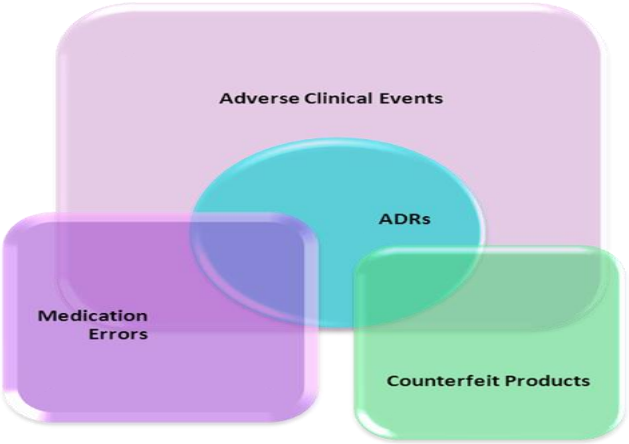

Figure 1: Medicine-related sources of Adverse Clinical Events [adapted and modified from 2]

Product Quality

The pharmaceutical products that have lost its pharmacological properties to cure or mitigate a disease are known as counterfeit products. A pharmacovigilance system monitors the availability of those kinds of products from the market place. Besides the counterfeit drugs, the system also monitors the manufacturing, storage and distribution of the adulterated medicine. There are several evidences throughout the world on the harmful effects caused by that type of counterfeit or substandard drugs. For example, almost 100 children died in Haiti after ingesting pain-relieving syrup adulterated with diethyl glycerol [3].The same incident occurred in Panama about 10 years later, killing over 120 people [4].

Medication Errors

Medication errors are caused by faulty systems and processes in a healthcare system. These problems can occur due to illegible handwriting by a physician or pharmacist, improper use of abbreviations, interactions of medicines, verbal miscommunications between patient and healthcare personnel etc. [2].

Medication errors often give rise to drug-drug interactions (DDIs), which is one of the preventable medication-related problems, yet it is one of the major causes of adverse drug reactions in clinical practice. Though prescription with multiple drugs increases the incidence of potential DDIs (pDDIs), it is a necessary practice in certain medical conditions as well as in certain group of patients, especially in elderly population [5]. It has been observed that in patients, who are taking 5 drugs at a time, have pDDIs of nearly 40%, and this figure increases to 80% when they take 7 or more medications [6].

Adverse Drug Reactions (ADRs)

These are the harmful responses that can be caused by a medicine even if it was given in recommended dose in a well-prescribed manner. These are, for example, allergic symptoms, withdrawal symptoms, or responses due to the drug-drug interactions [2]. A 'side-effect' or ADE, is a synonymous term to ADR, which indicates either of the beneficial, neutral or harmful effects caused by a drug other than its intended therapeutic effect. This term is sometimes used to describe minor or predictable ADRs (for instance, constipation with opiates) [7]. Adverse drug reactions are possible with any class of drugs. However, antibiotics and antitumor agents are the most troublesome classes of drugs which are responsible in causing 16% and 15% of all cases of ADRs [8]. Even the commonly used drugs can cause adverse drug reactions; therefore, safety of drugs is a prime concern in medicine. On the other hand, prescribing drugs in an 'off-label' manner can cause the incidence of drug toxicity [9]. Healthcare costs, which are resulted from these aspects, are considered to have negative impacts by the adverse effects of drugs, and

these impacts are severe in developing countries with larger population.

The need of pharmacovigilance

The preclinical data that is obtained from animal studies may not indicate the pharmacological effects on human as the physiology of human is largely different from that of animals in trial. On the other hand, the information that is obtained from a clinical trial may not be sufficient to study about a drug in a wider aspect. The people from different regions may differ from one another in terms of genetics, food habits, clinical practices, etc. Therefore, a clinical trial does not provide a detail picture about an ADR in its limited duration to a limited number of patients. Moreover, the rare ADRs are overlooked or cannot be identified in a clinical trial. Therefore, it is obligatory to have a constant watch on use of medicine, even in post-marketing period; in addition, better approaches must be devised for reporting and assessment and management of individuals who present with drug induced diseases [10].

The functions of a Pharmacovigilance Network

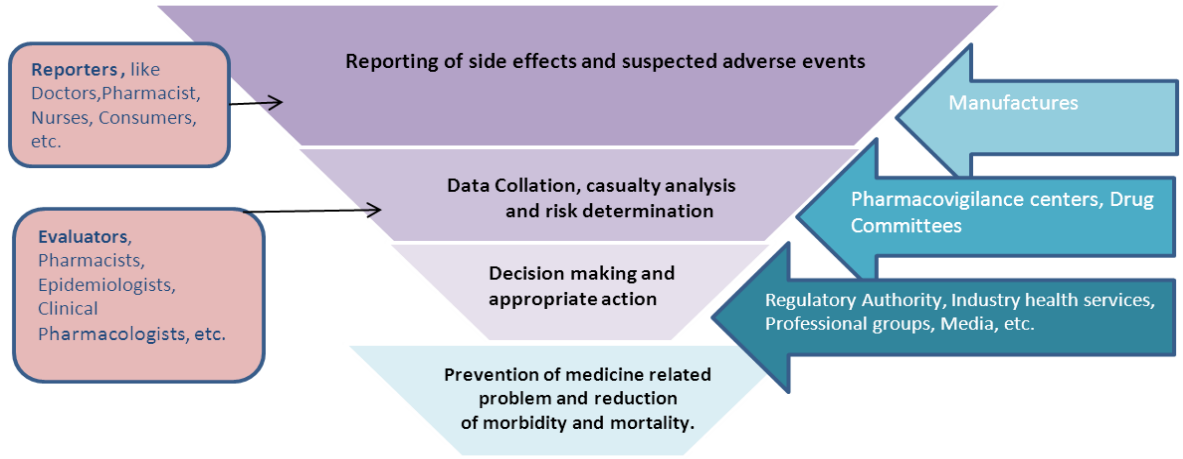

Figure 2: A Pharmacovigilance Framework [adapted and modified from 2]

A PV network is primarily based on three prominent aspects, such as manpower, structures and their systematic functions (**fig. 2**). The followings are the functions of a perfect PV network:

1. Promoting pharmacovigilance by collecting and managing adverse drug reports and reports on substandard and medication errors. It also works nationally and internationally for ADR monitoring activities.
2. Identifying signals of medicine safety for unknown medicines to medicines which are given in combination.
3. Assessing the risks out of an adverse effect and taking steps to manage those.
4. Identifying quality problems in medicines which may result in ADRs.
5. Ensuring effective public communication for proper using of medicines.
6. Incorporating outcomes of the health researches in a public health programmes and in national medicine policies.
7. Developing and maintaining drug utilization information.
8. Identifying issues regarding uncontrolled prescribing of medication and their distribution and also supporting to eradicate them [2].

To start a Pharmacovigilance network

Pharmacovigilance system is, in fact, built on a sound collaborative functionality. Besides those, the coordination and communications among different levels of the system and public relations are important landmarks (**fig. 3**). To setup a key model of a Pharmacovigilance network, the all-round support from political government is quintessential. Establishing of PV centres is governed by a government as the laws, funds, staffs, trainings and

overall developments depend on it. However, the setting-up and developing of a PV network are done with an aim of collecting information from local community and transferring them to country head center, which would collate the data gathered from the entire country and channel them to the Uppsala Monitoring Center (UMC), Sweden.

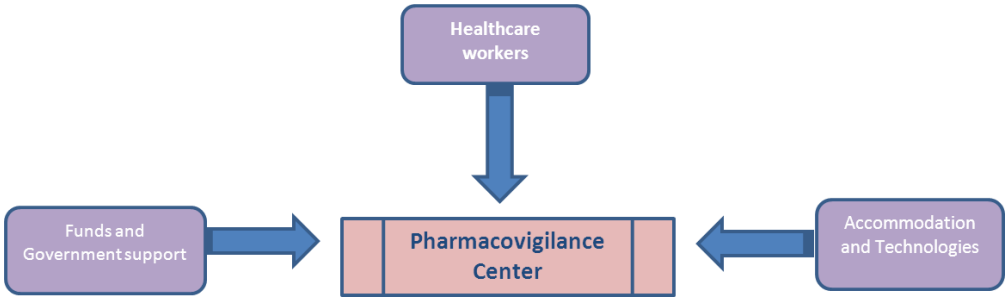

Figure 3: Constitution of a Pharmacovigilance System

The success of establishing an active pharmacovigilance network depends on several issues, but its activities are directly related with the development of the country's health care system and the number of health organizations involved with the setup.

So as to start a phamacovigilance network, promising monitoring centres should be set up at first. For that purpose, a suitable host is to be chosen initially. A governmental department, such as health authority, drug regulatory agency, professional body (like national medical association) or any other department, which is actively involved with patients, can serve the purpose well. There are many departments in hospitals or academic organizations with similar functions, for instance department concerning clinical toxicology or epidemiology, poison control unit, clinical pharmacy or clinical pharmacology department, etc.

It is essential to maintain an effective communication among the sub-centres of a network, and this effectiveness will contribute to enhance the performance of a network. To ensure this, presence of at least an apt professional in each of the participant organizations is required. Besides that, an effective communication, good public relation, co-ordination and collaboration among the sub-organizations are the keys for a successful network [2].

Minimum Requirements for a Pharmaco-vigilance network

The main goal of PV is to provide assurance for a safe use of medications. Thereby, in other words, it can be assumed that the main concentration of a PV network is to ensure 'patients' safety'.

To ensure this there needs certain requirements for its operations:

A. A well-organized drug safety management team: this is to increase the communication among the PV network. To assure an organized structure and smooth function, meetings among the PV practitioners, managers, technical agencies and donors should to be held time to time.
B. A national database: This gives the provisions for collating and managing ADR reports.
C. A national PV advisory committee.
D. Clear strategy should be specified for the communication in both routine and crises event communication.
E. Funding must be available to run different grounds of a network.

Basic steps in setting up a Pharmacovigilance Network:

Developing a general guidelines and setting up of pharmacovigilance centres are considered as the major steps to setup a pharmacovigilance network.

Developing general guidelines:

A general guideline is a standard strategy which confirms that the system or the PV services at all levels is up to the national and international regulations and

standards. There are some associated aspects with the followings:

- The general guideline for drug monitoring should be approved in the country.
- All healthcare professionals should be provided with copies of the guideline along with different forms of ADR controlling reports and case-reports.
- Constant contact should be maintained with the health authorities and bodies those are present locally and nationally.
- The printed materials should be produced to inform health professionals about aims and objectives of current PV set-up.
- There should be an adequate number of intellectual and experienced man power to run the system.

Setting up of Pharmacovigilance centres:

- **Establishing ADR centre:** These centres should have an official environment with staffs and accommodations, aided with facilities, such as telephone and fax, word processor, database management capability, bibliography, etc.
- **Communication process:** The importance of PV and its potential role in improving modern therapeutics should be informed to different level of health sectors via different means of communication.
- **Data acquisition:** A template for ADR reporting should be designed, and the availability of it to different departments of a hospital should be confirmed.
- I**nternal education:** Education or knowledge of pharmacovigilance staffs should be sound regarding data collection and verification, coding of drugs, case causality assessment, signal detection, risk management, interpreting and coding of adverse reaction descriptions, etc.

The expertise should have a strong background either in clinical medicine, pharmacology, toxicology or epidemiology. At the start a pharmacovigilance centre may be run by part-time expertises and their assistants, but soon it should be replaced by full-time specialists, who can be a pharmacist or a physician [11].

- **Establish a database:** An easily retrieval and confidential database should be created to store data safely.
- **Promotion:** Promotional measures should be taken to let the patients and health professionals informed about the importance of reporting adverse drug reactions and drug safety through medical journals, professional publications, and meeting or seminars. These are all done to inculcate a habit of reporting of ADRs to healthcare practitioners.
- The centres should also be associated with conducting research on pharmacoepidemiological studies on specific drug related problems.
- N**etworking:** Steps should be taken to work in collaboration with the international drug monitoring bodies.
- **Advisory Committees**: A pharmacovigilance centre must be aided with a committee. This is to support the pharmacovigilance centre with various procedures, such as data collection and assessment as well as for publication of information.
- It is highly expected to have multi-disciplinary expertise in the advisory body. The prime privilege of setting up a pharmacovigilance centre nearby to a hospital is to get the easy access of number of expertise from various fields.
- **Poison Control and Drug Information Centres:** The functions of a pharmacovigilance system and a poison control or drug information centres have much in common in organisational and scientific points of view. If pharmacovigilance centres are started in collaboration with poison control or drug information centre, the function of the centres will be more stimulatory as they will be able to share different facilities, knowledge and activities [2].

Capacity building for Pharmacovigilance Network

In order to ensure the proper functioning, development, efficiency and sustainability in a pharmacovigilance network, there requires building up of institutional capacities. This capacity building process can only take place when the institution is

built upon an appropriate policy and legal framework. The capacity building processes include the management of the health products, the system and individual in the network, and effective monitoring of medicines with a safety perspective. The aim of the capacity building is to create a robust system without creating changes in social structures, resources, technologies and personalities. The figure below (**fig. 4**) depicts the related elements needed in a pharmacovigilance network to achieve a fully effective drug monitoring body. The proper coordination and management among the four strata are needed to build capacity for the network.

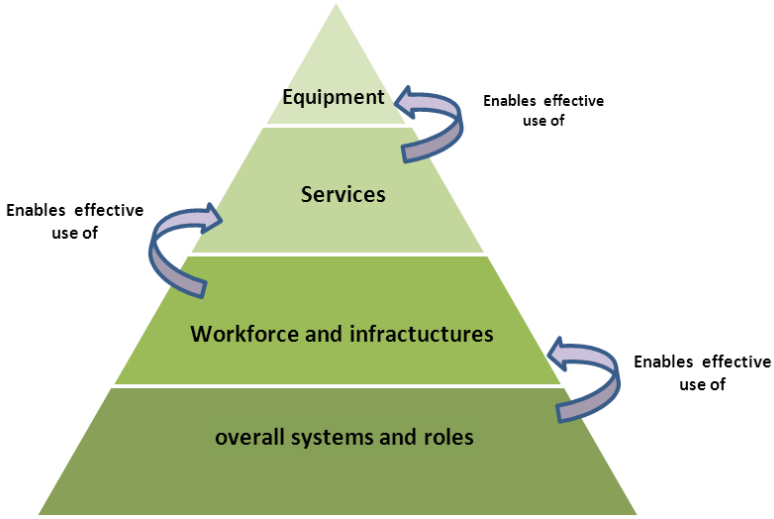

Figure 4: Capacity Building for a Pharmacovigilance Network [adapted and modified from 12]

Data acquisition by a Pharmacovigilance network

A pharmacovigilance network collects information from different parts of a country. This spontaneous reporting becomes a major source of information for a pharmacovigilance network.

ADR reporting form

A 'report' in PV is defined as "a notification relating to a patient with an adverse medical event (or laboratory test abnormality) suspected to be induced by a medicine."

A case report form contains the following information to take information upon:

1. A patient's details, which includes the age, gender and medical history, ethnicity etc.

2. Details regarding the adverse events, including the nature, characteristics, and severity of the adverse reaction.

3. Details of the **s**uspected drug or vaccines must be included along with the name of the medications taken at the same time.

4. The patients are also required to fill-up the sections on their risk factors.

5. Name and address of reporter should be kept confidential and are used for the follow-ups or the data verification.

ADR Reporting

Medias, such as professional journals, drug bulletins, fax, emails, and telephone should be chosen to harness the feedbacks from different levels of a society, regarding the adverse effects of drugs. The proper and uninterrupted distribution of the reporting forms must be ensured to the professional and consumer levels, and the supply should be monitored time to time. The steps should be taken to keep the price lowest for the reporting forms. The strategies such as 'free-post' or 'business reply' should be arranged [13].

Professionals working at different sectors of healthcare system are targeted as the prime source of information for PV practice.

The pharmaceutical manufacturers are primarily responsible for the safety of their products. The adverse reactions that occur out of a pharmaceutical product are expected to be notified to the competent level, but the patients are also encouraged to report to their doctors for this purpose.

There are different aspects to achieve an efficient reporting. The minor side-effects are given more emphasis in the case of a new drug; whereas, the major or rare side-effects are sought to be reported in case of established drugs. Not on the medicinal products, but the side-effects out of the cosmetic products or the alternative medicine are also reported [13].

Stimulation of reporting and bringing reporting culture

To get more feedbacks from the healthcare professionals, stimulation of the process is very essential. And these stimulations must go on continuously. The first and foremost thing is to achieve the positive attitude of the health professional towards the pharmacovigilance activity [10].

There are various ways by which this right attitude can be brought about. The easy availability of the reporting form is a vital way to promote the trend. Besides that, there should be some provisions to accept the ADR reporting via personal letter, phone, emails; these actually make the way of reporting much convenient. Moreover, involving the pre-and post-graduate students in the activities of PV practice, increases the efficiency as well as promotes the public awareness for the pharmacovigilance activity. On the other hand, creating collaboration with the drug related society and the professional associations can stimulate the process of reporting in a PV network. In addition, to that integrating the activities of pharmacovigilance activities with the activities of Clinical Pharmacy and Clinical Pharmacology is a major step to enhance the effectiveness of a PV activity [13].

Signal detection

WHO defines the 'pharmacovigilance signal' as "reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously" [13].

Signal detection is one of the major objectives of PV; moreover, the efficiency depends on the effective detection of the signals. This is done by means of retrospective counting of the incident of ADEs. The aim of the signal detection is to utilize the information gathered to identify and manage an occurrence of adverse events.

The pharmacovigilance network can work with the automatic signal generation techniques. Automated signal generation is an emerging method for signal detection which facilitates spontaneous reporting. This is based upon the comparison of report with the reported safety profile of other products. One of the examples of those methods is "Bayesian Combination Propagation Neural Network". This is used by the WHO Uppsala Monitoring Centre; whereas, the FDA uses the "Modified Gamma Poisson Shrinker Method". Automated systems create better signal detection standards and help the detection and analysis of signals, savings money, time, and manpower [13].

On the other hand, the detection techniques can be aided by simple methods of epidemiological and statistical tools which should generally be aided with rational clinical assessment. It is to be noted here that to have an efficient pharmacovigilance model, it is essential to have an easy notification technique [13].

Relations with other parties

1. **The Drug Regulatory Authority:** This regulatory body should always be notified about the observed adverse reactions time to time which may include cases with particular interest. However, there must not be any delay of performing that in case of unusual or serious conditions.
2. **Pharmaceutical companies:** The pharmaceutical companies need the same information as they are required by the regulatory bodies. The companies should be made aware of the possible adverse effects by direct means or via regulatory authority.
3. **Professional medical and pharmaceutical associations:** Cooperation of PV centres and these types of bodies form the core of a pharmacovigilance system. They are always given the priority to be informed such that they can undertake preventive measures whenever it is necessary.
4. **WHO and its collaborating bodies:** A new PV network must make constant contacts with the World Health Organisation**,** Geneva and the WHO

collaborating centre for International Drug Monitoring, Sweden.

5. National Pharmacovigilance Centres: It is always beneficial to have collaboration with the national pharmacovigilance centres of nearby countries. This is as because of the fact that when in emergency, they can provide assistance in terms of manpower or intellectual support. Sometimes they can train the staffs in their centres.

6. Academia: The participation of the PV experts from an academic institution can promote the objectives of a PV network. The findings of a pharmacovigilance centre can influence the researchers from an academia to find out more on the cause and way of prevention.

7. Media and consumer organisations: The journalists and other medias can be helpful to manage the risk when there initiates an acute drug problem. They are also helpful in creating general public awareness related to drugs.

Funding

The size of the population that the pharmacovigilance network has to deal with and the rate of reporting govern the estimation of the money needed to run the whole network. The collection of data from the root level of the society also involves good expenditure. To run a number of centres within a large network calls for basic and regular source of funding. The funding can be obtained from the drug regulatory authority. In addition to that, various parties, such as university departments, health insurance companies, and professional associations can be a good source of funding.

CONCLUSION

The management of the ADRs of drugs is a very essential area for a nation to take concern on. This is because - the causes of ADRs can lead to adverse clinical as well as economic consequences. All the institutions in a health sector must collaborate among themselves in order to reduce the harm that can be caused by ADRs; all round efforts are expected to put by them if any catastrophic adverse drug event occurs ever. PV is the central idea that will enable a country to monitor on safety aspects of medicines and arrive at tailor made regulatory decisions for its population. A pharmacovigilance network is the concept which can serve to build all round developments needed to reduce the incidence of the medicine-related harms on public health. Establishing an efficient pharmacovigilance system is a mounting task which needs thorough planning, efficient approach, enthusiasm and motivation from the members. Once it is accomplished, we can ensure a better present and also a secure future.

REFERENCES

1. World Health Organisation (WHO). The importance of pharmacovigilance: safety monitoring of medicinal products (2002). Essential Medicines and Health Products Information Portal. [*online*] http://apps.who.int/medicinedocs/en/d/Js4893e/ [Last accessed on: 18th, Oct, 2013].
2. Strengthening Pharmaceutical Systems (SPS). Supporting Pharmacovigilance in developing countries: the systems perspective. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health. 2009; [*online*] http://apps.who.int/medicinedocs/documents/s18813en/s18813en.pdf [Last accessed on: 18th, Oct, 2013].
3. O'Brien KL, Selanikio JD, Hecdivert C, Placide MF, Louis M, Barr DB, Barr JR, Hospedales CJ, Lewis MJ, Schwartz B, Philen RM, Victor S, Espindola J, Needham LL, Denerville K. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. *JAMA* 1998; 279 (15): 1175–80.
4. Bogdanich W and Hooker J. From china to panama, a trail of poisoned medicine. 2007. [*online*] http://www.nytimes.com/2007/05/06/world/06poison.html?pagewanted=all&_r=0 [Last accessed on 16th, Oct, 2013].
5. Sitar DS. Aging issues in drug disposition and efficacy. Proc West Pharmacol Soc. 2007; 50:16–20.
6. Grattagliano I, Portincasa P, D'Ambrosio G, Palmieri VO, Palasciano G. Avoiding drug interactions: here's help. J Fam Pract. 2010; 59:322–329.
7. Ferner RE, Butt TF. Adverse drug reactions. Medicine 2012; 40(7):366–370.
8. Novotny J, Novotny M. Adverse drug reactions to antibiotics and major antibiotic drug interactions. Gen. Physiol. Biophys 1999; 18:126–139.

9. Misbah HM, Kundlik G, Ranju P, Sugra SS. Incidence of adverse drug reactions in a tertiary care hospital: a systematic review and meta-analysis of prospective studies. Der Pharmacia Lettre. 2010;2(3):358–368.
10. Chakrabarty M and Thawani V. Starting a pharmacovigilance center: actions for implementation. Journal of Pharmacology and Pharmacotherapeutics 2011; **2**(4): 295–299.
11. Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol 2003; 57:127–34.
12. Potter C, and Brough R. Systemic capacity building: A hierarchy of needs. Health Policy Planning 2004; 19: 336–45.
13. Uppsala Monitoring Center (UMC). Safety monitoring of medicinal products: Guidelines for setting up and running a pharmacovigilance centre. 2000; [*online*] http://apps.who.int/medicinedocs/en/d/Jh2934e [Last accessed on: 16th, Oct, 2013].