A Review on Interrelation among Post-authorisation study, Regulatory action and Pharmacogenetics in Pharmacovigilance

A project submitted

By

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To

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Dedicated to my parents for their endless love, support and encouragement.

Certification Statement

This is to certify that this project titled "A Review on Interrelation among Post-authorization study, Regulatory action and Pharmacogenetics in Pharmacovigilance" submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Dr. Mesbah Talukder, Associate Professor, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Countersigned by the supervisor,

_____

Abstract

Pharmacovigilance system is the recent approach to control the incident of ADRs which is hazardous for patients both physical and mental health. Researchers are continuously trying to develop methods that can predict the ADR before it occurs and assure the patient's safety. The global scenario of this system is more advanced compared to Bangladesh and getting stronger day by day. Pharmacovigilance method can be described as the fusion of administrative action, clinical trials, studies done on authorized drugs, pharmacogenetics, epidemiology, signal detection and management, statistics, IT sector, maintaining database etc. However, the main focus of this paper is to detect the liaison among post-authorisation safety check, genetic factors and enactment of laws in the evolvement of pharmacovigilance system. The findings of the study can help to show a huge scope in the advancement of pharmacovigilance.

ACKNOWLEDGEMENT

First and foremost, I am ever grateful to Allah, the Creator and Almighty, for giving me the potency, knowledge, capability and opportunity to undertake this research study and complete it satisfactorily. Allah has given me the power to believe in my passion and pursue my dreams. Without His blessings, this achievement would not have been possible.

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List of Abbreviation

FDCA - The Federal Food, Drug, and Cosmetics Act

FDA - Food and Drug Administration

ADR - Adverse Drug Reaction

EU – European Union

ADE - Adverse Drug Event

ME – Medication Errors

ICSR - Individual Case Summary Report

OMOP - Observational Medical Outcomes Partnership

AERS - Adverse Event Reporting System

VAERS – Vaccine Adverse Event Reporting System

NRA - National Regulatory Authority

ADME – Absorption, Distribution, Metabolism, Excretion

DHPL- Biologicals with a Dear Healthcare Professional Letter

DHPC- Biologicals with a Direct Healthcare Professional Communication

Chapter One: Introduction

1.1 Pharmacovigilance:

Pharmacovigilance becomes the new challenging area in modern medical system. In this era of advanced technology, the health care facilities are moving forward in such a position that people are now fighting against death. According to WHO, the term pharmacovigilance can be defined as a system performing to investigate, analyze, predict and avert the ADR or problems associated with the use of drug.The adverse drug reaction, adverse drug effect and adverse drug event all these terms are related to pharmacovigilance. FDA defines "An adverse drug reaction includes any pathological state provoked by a medicine having no alliance with the nature of the drug and the conditions for which it arise, i.e., overdose related complications, therapeutic, accidental, homocidal; hypersensitivity; allergy; or injury from improper technique of administration, use of the wrong drug, error in compounding, labeling, or packing, or other error in the manufacturing of the drug , or from the preparation for use in the hospital" (Hassan, 1986).

Clinical trials before approval of any drug or medicine for marketing looks for potential threats for using the drug or medicine in particular situation or treatment basis. As these clinical trials have been done with small sample, these can't explain all the cases. In order to maintain the safety of patients the new term pharmacovigilance has been introduced which includes the continuous ADR (Adverse Drug Reaction) monitoring and reporting, arranging different studies (e.g. observational studies, cohort studies, Non-interventional studies) to identify the factors for adverse drug event, making strategies to eliminate the chance of ADR, defining mechanism of ADR and therefore ensure the safe use of drug worldwide. Post-authorisation studies are mainly done with authorized drug to check that is there any threat to use the drug or not. If any injurious effect or reaction has been found the drug has been withdrawn from market and further studies have been initiated to make it safe. From the history, we found many examples of fatal or dangerous ADR of drugs which give rise to exigency to take initiatives immediately.

1.2 History of pharmacovigilance :

Around 1961-1962 world faced a most terrific event caused thalidomide, the drug which has been promoted as a safe, effective drug and mostly used in early pregnancy. Unfortunately, the drug has been identified as teratogenic when it was too late. Around 10,000 birth defects was reported due to use of that drug (Andrews & Moore, 2014). Another tragedy took place at the beginning of 1970s where a multi-system disorder (oculomucocutaneous syndrome) caused by the a cardiovascular drug named practolol (Neutel, 2009). These several events finally came to the sight of authorities and they decided to implement drug monitoring system for newly marketed or invented drug to avoid such life threatening or hazardous adverse drug effect. But there were so many factors or consideration they learnt when authorities get down to the field. The concept of pharmacovigilance is too broad and its development and implementation took many years of work ship and research which still under evolving in multiple perspectives.

1.3 Approval processof medicine:

To detect and manage the adverse drug event there is a need for multiple series of studies. In this time after any drug has been approved for marketing as a generic, the drugs are introduced in the market under proper observation and studies. These studies are mainly known as post-authorisation studies which have two broad parts: post-authorisation efficacy and post authorization safety study. Post-authorisation safety studies mainly related with the pharmacovigilance.

The stages of drug approval from drug discovery to market authorization completely summed up in the figure 1.1

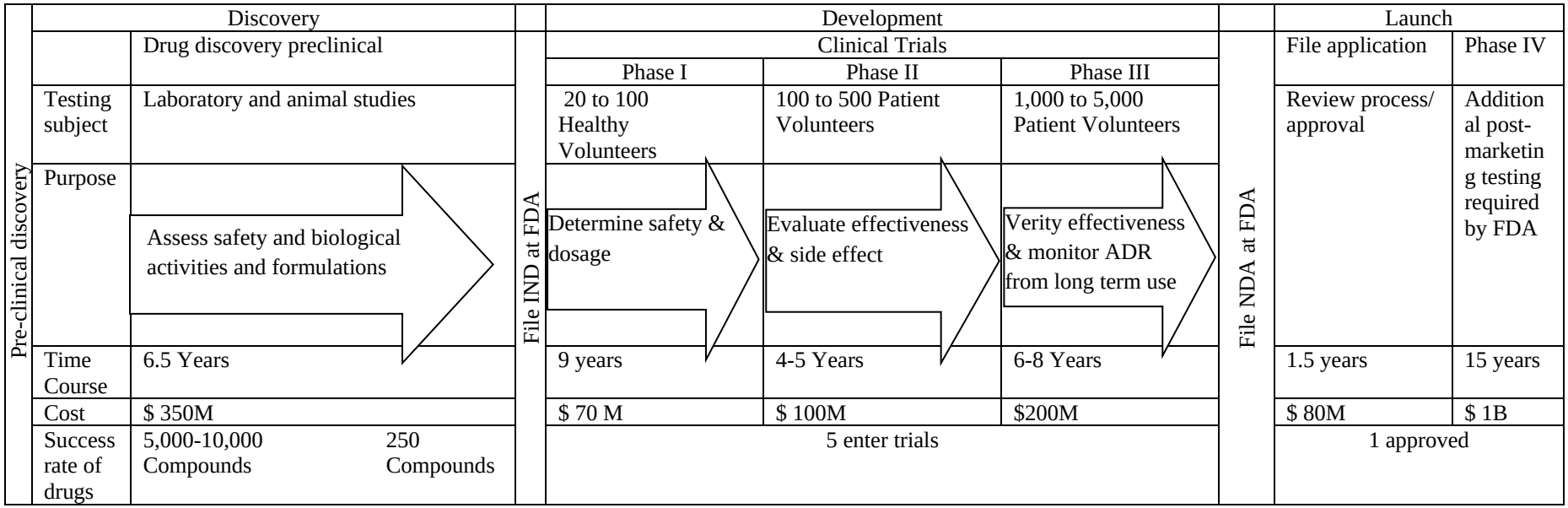
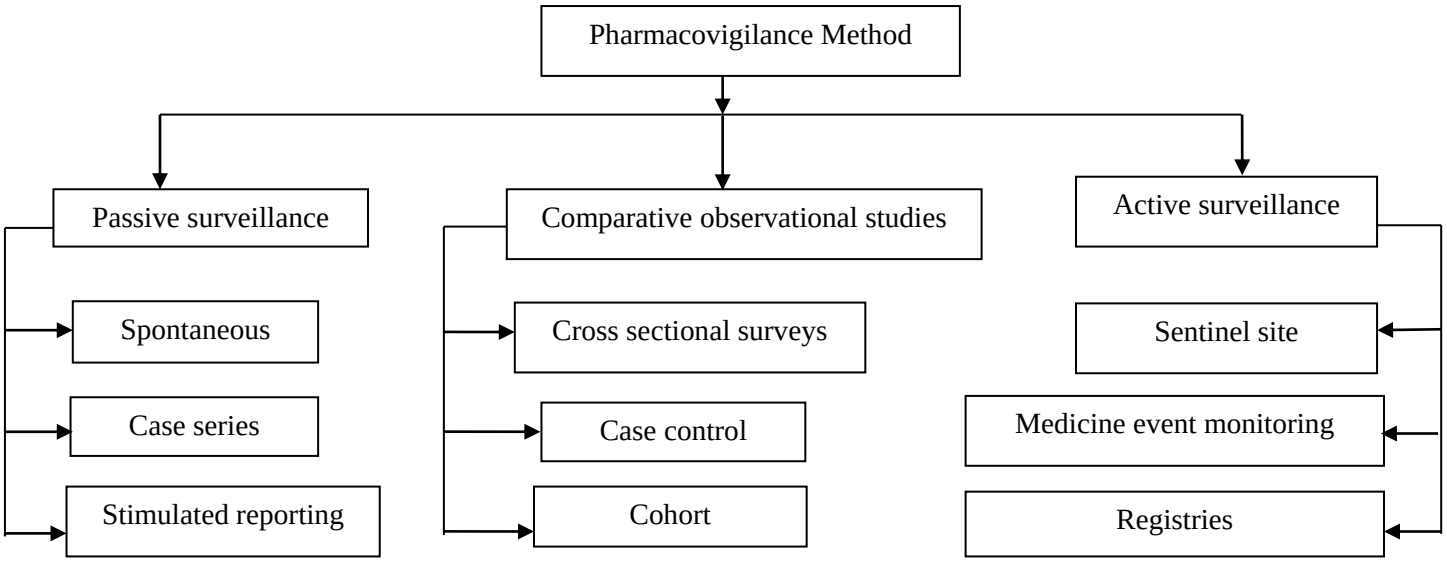


Figure 1.1: An overview of drug development and approval. Figures available at http://www.biology.iupui.edu

Drug discovery, development and approval is a long and risky road which is considered as the most complex process can be subdivided into various small tasks and functions. The process can be broken down in three major stages – drug discovery, drug development and market launch. Firstly, drug discovery covers all the experiments and studies planned to identify compounds having clinical effectiveness to treat a particular or several diseases. In this stage, 5000-10000 compounds have been evaluated to specify their biological activities and finally 250 compounds have been selected for the pre-clinical trials. Drug development stage consists of clinical trials having phase I, II, III done with the 5 selected compounds after pre-clinical studies. Finally, one compound has been approved as a drug and authorized to be marketed to serve its purpose to treat disease. After launching the drug into the market, phase IV clinical trials have been started to observe the safe use of drug and control any undesired ADR and keep it under record to conduct further research on it to ensure the complete safety. From the figure, it has been also found that post-authorisation study of a medicine is not a single process but a combination of multiple processes which have been done in almost 15 years to check the possible occurrences of ADR and observe the effect of drugs in their long time uses(Blass, 2015).

1.4Pharmacovigilance methods:

There are a number of methods to run a pharmacovigilance program. According to WHO, the methods of pharmacovigilance study can be described as follows -



Pharmacovigilance method can be classified into three broad categories-

A. Passive surveillance

- Spontaneous reports:

A voluntary system which detects ADRs in patients taking medicines. Here, the data has been collected are not obtained from any study or research.

- Case series
- Stimulated reporting:

Approach practiced to inspire and aid to reporting signals of a new drug by doctors, physicians, pharmacists and nurses in a specific health care settings for a limited period of time

B. Active surveillance

Inquire the accurate number of ADE from a methodized system.

- Sentinel site :

Auditing the archives of the hospitals or consulting with the patients and physicians to assure that the entire and precise information about reported ADE have been obtained.

- Medicine event monitoring:

Studies conducted through continuous inspection

- Record:

Prepare portfolio depending on the nature of pathosis and treatment

C. Comparative observational studies

Consists of several observational studies intended to confirm alert

- Cross sectional surveys

- Case-control
- Cohort (Black, Tagiyeva-Milne, Helms, & Moir, 2015).

The major objective or goal of a health care system is to maintain patient's safety where the appropriate and safe use of drug or medicine is the most concerning aspect. Because of a severe ADE of a drug, patient may lead to a more emergency condition or even death can happen where the actual disease of that patient was not that much serious. Even a use of drug can create heavier risk for the upcoming generation as some drug can passes through placenta or can be delivered to the child during breastfeeding. We have found such incidence in the past and then the development of pharmacovigilance program started as a response of those incident. The basic concern of pharmacovigilance has been modernized according to the experience or lessons from previous.

To create an appropriate complete safety profile of a drug needs a huge data about the use of drug and every individual case and ADE. The data sources used for the safety monitoring of a drug in post marketing environment are given as follows-

Table 1.1: Identified data sources to evaluate product safety in the post-marketing setting (Sharrar & Dieck, 2013).

Data source	**Activities**
Passive surveillance	
ICSR	Individual case review
All ICSRs	Aggregated analysis
Selected ICSRs	Case series
VigiBase, AERS, VAERS, Eudravigilance	Disproportionality analysis
Active surveillance	
Electronic health records	Observational studies
Sentinel initiative	
OMOP	
Registries	

1.5 Factors influence the causality of ADR:

Analyzing the data of various research work and cases scientists have been found some factors that influence the susceptibility of the casualty of ADE such as -

• Lifetime – the aged and newborns are more prone to
• Sex – in general females are at great danger
• Epidemiology– can impact drug metabolism.
• Excretion hampered– decreased excretion through liver and kidney
• Pathological condition – e.g. asthma
• Using more than one drug at a time, may lead to potential drug interaction
• Any record of an ADR previously(Andrews & Moore, 2014).

A research article about "Consequences, measurement, and evaluation of the costs associated with adverse drug reactions among hospitalized patients in China" shows – Among 2739 ADR diagnosed where it indicates 0.81% ADR rate, the total socio-economic cost was calculated at ¥817401.69, in which the straight expense was ¥603252.81 and the ambiguous expense was ¥214148.88 (Qing-ping et al., 2014).

As the absolute safety is unobtainable, so the prime objective of pharmacovigilance is to draw an acceptable safety level of a drug. There are some factors which determines the level of acceptance which are-

• The degree of entire danger(s) and the possible physical state
• The outcome(s) aimed, also calculated in pure terms
• Demureness of the illness for which thetherapy is required
• The uncertainty and advantage of substitute direction
• The personal context who has been given the treatment (Andrews & Moore, 2014).

The main goal of phamacovigilance development is to prevent or take steps that can prevent or minimize the incidence of ADR in a maximum level. There are some factors which stimulate the prevention of ADR and these can be broadly classified as –

1. <u>User characteristics:</u>

• Demographics: age, sex, race
• Genetic factors: polymorphisms (e.g. acetylator status)

• Concomitant diseases (e.g. impaired hepatic or renal failure)

• History of previous ADRs (e.g. allergy)

• Compliance

2 Drug characteristics:

• Route of administration

• Formulation (e.g. sustained vs. immediate release, excipients)

• Dosage regimen

• Therapeutic Index

• Mechanisms of drug metabolism and route of excretion

• Potential for drug interactions

Based on these possibilities, a wide variety of potential actions may be considered and in various combinations (Neutel, 2009).

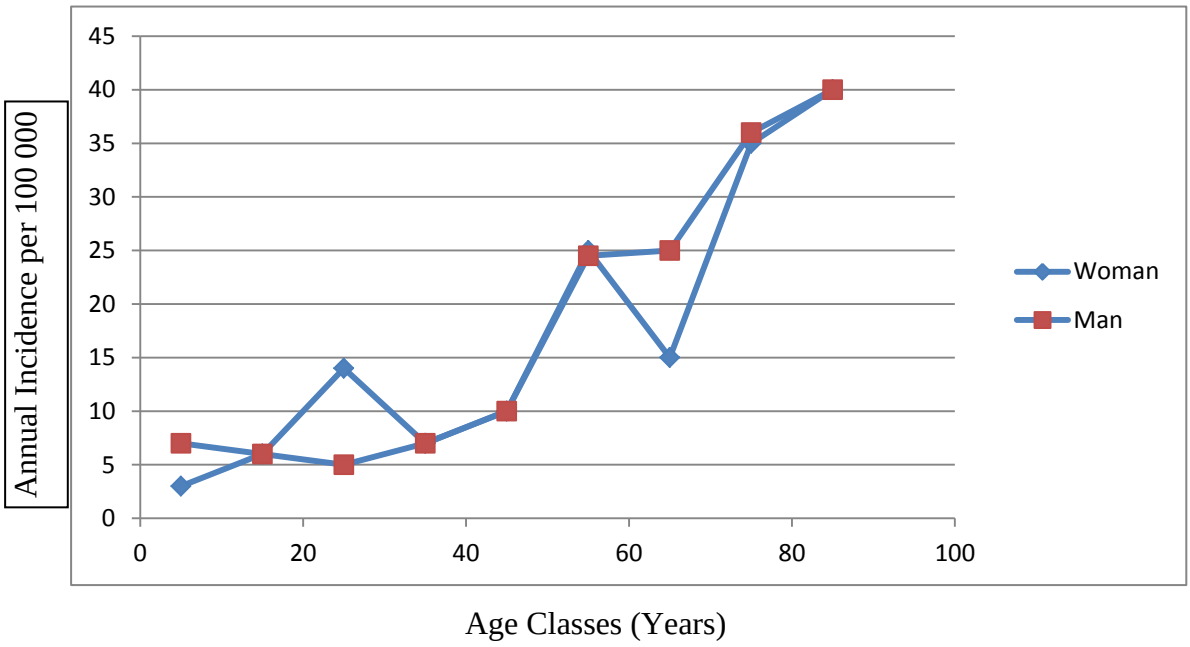


Figure 1.3 : Incidence of severe ADRs depending on sex and age (Montastruc, Lapeyre-Mestre, Bagheri, & Fooladi, 2002).

Here, figure 1.3 shows how the casualty of ADR varying with the gender and age. From the graphical presentation it can be assumed that there is no significant variation of causing ADR according to gender but the causality of ADR can vary depending on the age. In the

graph the incidence of ADR is lower for children but higher incidence found for the aged person (specially> 80 years).

1.6 Significance of ADR reporting:

As the term pharmacovigilance deals with the management and prevention of ADR, the reporting of ADR is mandatory. The health care professionals must have to know what type of or which ADR the must report to the national authority. Generally, the physicians, nurses and pharmacists are bound to inform

- Life threatening ADRs
- ADRs that are not included in the product insert
- ADRs results from the use of a new drug generally < 2 years after authorization except those are already mentioned in the SPC
- Frequently occurring ADRs or there is chance to occur the ADRs frequently (Rydberg et al., 2016).

The patients can also report ADR along with the health care professionals (examples – physician, pharmacist, nurses).The types of source that can contribute to the pharmacovigilance database are shown below-

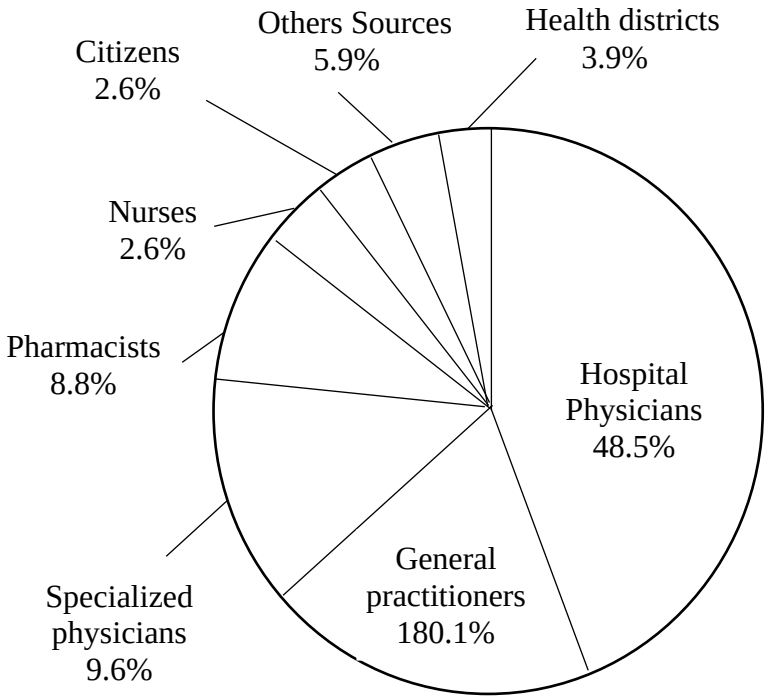


Figure 1.4: Origins of ADR reports of Italian pharmacovigilance database from 2004 to 2010 (Conforti et al., 2012).

In the figure it has been confirmed that the most reliable and available source of ADR reporting is general practitioners. However, hospital and specialized physicians, pharmacists and nurses also play a vital role for reporting and detecting ADR signals effectively.

The information that has been found from the ADR reporting is needed to improve the prescribing pattern and manage the preventable ADR more efficiently. The researches which have been done to explain the anticipated obstacles to reporting ADE in hospitals founds that though nurses and pharmacist are well known about ADR reporting, they have lack of knowledge about the ADE reporting guidelines.

1. Expertise	:	Deficit of ability of recognizing the reported situation
		Inadequate learning about definitions
		Insufficient insight about protocol
2. Intelligence	:	Incompetence to contrast ADRs and MEs

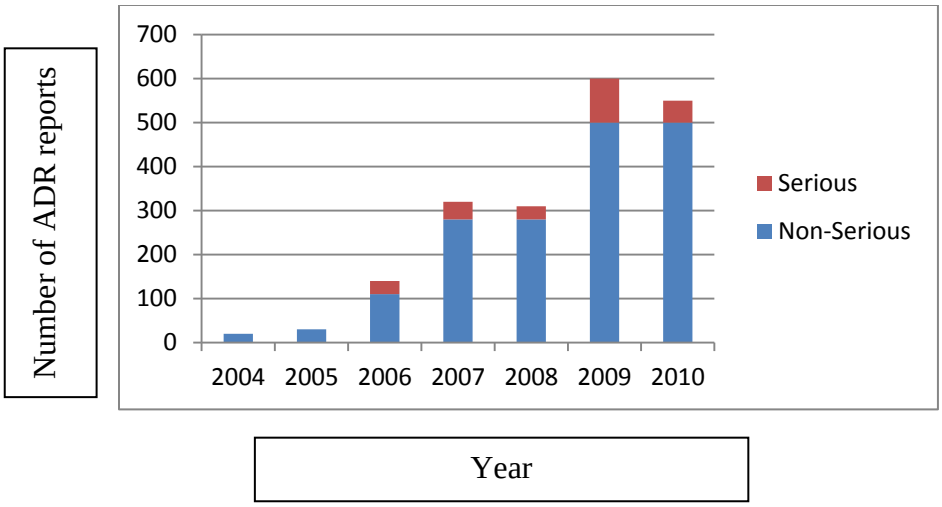
3.Faith about results	:	Scared of being penalized or blamed
4. Motivation and goals	:	Limited response
		Less ambition
		Excessive duty
		No inducement
5.Circumstantial	:	Shortage of ethological assets
discipline		Deficit of time needed for reporting accurately
		Puzzling yellow card
		Complex system for legislative reporting
		Insufficient ease of reporting
		Shortage of clinical pharmacists
		Restricted path to yellow card scheme
6. Public domination	:	Absence of partnership
		Inappropriate support of the managerial system and teammate in the hospitals

(Mirbaha, Shalviri, Yazdizadeh, Gholami, & Majdzadeh, 2015).

The actual scenario of pharmacovigilance system all over the world can't be estimated by analyzing several studies, it needs a lot more data to describe or explain the development as every country does not have same standard or qualification to run the system.The patient's consciousness or the qualification of healthcare professionals is also varying country to country. The governmental involvement or concern is also an essentialcomponent to the improvement of ADR reporting, prevention & management.

One report has been published by analyzing the Italian database of pharmacovigilance about ADR reporting by nurses and the result has been shown graphically -

A



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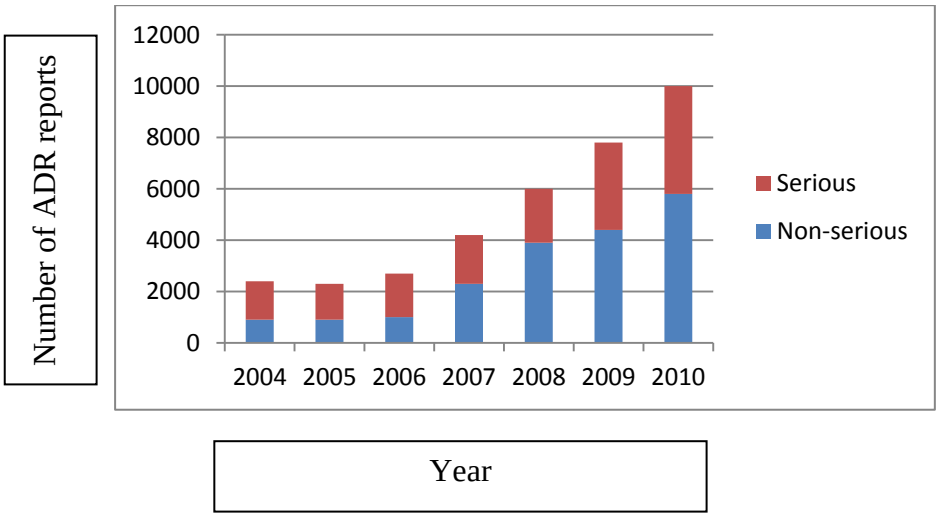

Figure 1.5: Annual figure of intense and non-serious ADR reported (A) by nurses and (B) by hospital physicians in the Italian pharmacovigilancefrom2004 to2010 (Conforti et al., 2012).

The charts show that the number of serious ADR reporting by physicians is higher than the serious ADR reported by nurses. Furthermore, non-serious ADRs have been reported more than the serious ADRs.

Numerous researches have been conducted which are related to the pharmacovigilance system. Results from some studies are focused in the following-

Table 1.2 : Characteristics of studies examining ADRs in the aged person (Alhawassi, Krass, Bajorek, & Pont, 2014).

Reference	Country Year conducted	Size (N)	Mean age (Year)	Design	Setting (Specialty)	Prevalence (rate)	Identification method
Conforti et al	Italy 2009	1,023	81.9	Prospective cross-sectional	Geriatric	36.2%	Systematic medical review
De Paepe et al	Belgium 2007	80	76	Prospective cross-sectional	Emergency	46.3%	Systematic medical review
Franceschiet al	Italy 2004-2005	1,756	Not Reported	Prospective cross-sectional	Geriatric	5.8%	Physician reported
Hellden et al	Sweden 2002	154	82.1	Prospective cross-sectional	Emergency	14.3%	Systematic medical review
Kojima et al	Japan 1995-2010	2,412	78.7	Prospective cross-sectional	Geriatric	10.4%	Physician reported
Laroche et al	France 1994-1996 1997-1999	2,018	85.2	Prospective cross-section al	Geriatric	19.1%	Systematic medical review
Lattanzio et al	Italy 2009	506	80.1	Prospective cross-sectional	Medical	11.5%	Systematic medical review
Ma et al	China 2008-2011	4,760	87.5	Prospective cross-sectional	Emergency	6.9%	Physician reported
Marcum et al	USA 2004-2006	678	76.4	Prospective cross-sectional	All admissions (veterans)	10.0%	Systematic medical review
O'Connor et al	Ireland 2010	513	77	Prospective cross-sectional	General medical and surgical	26.3%	Systematic medical review
Olivier et al	France 2002-2003	789	80.2	Prospective cross-sectional	Emergency	8.4%	Physician reported
Sikdar et al	Canada 1995-2007	64,446	Not Reported	Prospective cross-sectional	All hospital admissions	6.3%	Physician reported
Tangiisuranet al	UK 2007-2008	560	87.1	Prospective cross-sectional	Geriatric	13.2%	Systematic medical review

In the table, the highest prevalence rate of ADR is 48.3% found in Belgium and lowest rate is 8.4% found in France for emergency care unit.

1.7 Effects of ADR on patient:

The effect of ADR on a patient is not only physiological; the patient experiencing ADR from a medicine faces various psychological condition such as fear, doubt, frustration and anger etc.It has been found that the patient taking long-term medication is more aware of ADR than the patient having short course medication (Lorimer, Cox, & Langford, 2012).

Many more research has been conducted to show the casualty and preventability of these ADR related to any medicine intake. In emergency care setting it has been found that some ADRs are successfully reduced by avoiding the use of some drug combination, anticipation of dose depended side effects, considering individualized dosing system(Rydberg et al., 2016).

A study has been arranged to estimate the percentage of patient with preventable ADR. By analyzing the some studies they have claimed that 45% of ADRs are preventable. The result have been interpret by using meta-analysis method in eight studies having total 24128 inpatients (Hakkarainen, Hedna, Petzold, & Hagg, 2012).

1.8 Regulatory pharmacovigilance :

The regulatory actions taken by authorities flourished the pharmacovigilance practice in an exalted level day by day. In modern times, authorities and people are much more concern and aware about adverse drug event or other complications associated with the use of medicine. The advanced practice of pharmacovigilance makes the smooth way to success in controlling or avoiding adverse drug reaction effectively.

Establishment of pharmacovigilance need appropriate regulations and authorization to go ahead. The necessity of drug regulation first acknowledged after the incidence of thalidomide. Though pharmaceutical companies have complete guidelines according to legislation, these regulations are hardly followed to assure safe use of drug(Neutel, 2009). The consequences of thalidomide also fetch a percipience to make changes in FDA’s focus and as a result, FDCA was legislated in

1938 by FDA. FDCA initiates the government involvement to determine the risk-benefit ratio of any drug. Before FDCA, the world had limited administrative action to examine the medicinal product in terms of safety and efficacy, no control on the production and very few penalties for the scam and disaster (Andrews & Moore, 2014).The indispensable role of medicine legislation is perceived widely and many countries adopt thesystem to preserve the public health and safety of every patient. Though the outline of pharmacovigilance system differs from country to country, the main focus is same.

EU legislation is the exemplary initiative for every nation. At the beginning, EU legislation proposed by the European Commission and went through various processes finally emerged via EU parliament.EU medicines legislation has two broad aims – protection of public health and the creation of a single market for pharmaceuticals. The exigent principles currently specified in the EU legislation may be summarized as follows:

- " Pharmacovigilance is based on existing national systems
- The European Medicines Agency (EMEA) is responsible for co-ordination
- Member States are responsible for conducting pharmacovigilance in their own territories
- The common forum is the Pharmacovigilance Working Party of the Committee for Human Medicinal Products (CHMP)
- MA holders have defined responsibilities"(Neutel, 2009).

After the adverse effect of thalidomide the world felt the need of developing regulatory actions related to specific safety study before marketing and post marketing or post-authorisationpharmacovigilancestudies including reporting requirements, gathering information into reviewable databases, and installation of pregnancy registries. All these activities indicates a combined attempt to recognize the drug safety signals at the very beginning and start to know the drug associated disorders(Andrews & Moore, 2014).

Every single day researchers are trying to develop an appropriate and effective methods and systems for pharmaovigilance. Though so many suggestions have been proposed, it is difficult to implement one standard method or regulatory actions all over the world. Every country varies

from each other in term of economics, lifestyle, socio-economic value, technological development, educational status and quality and other issues. In the following figure 1.5 shows a proposed process for national regulatory authorities for react to emerging safety issues.

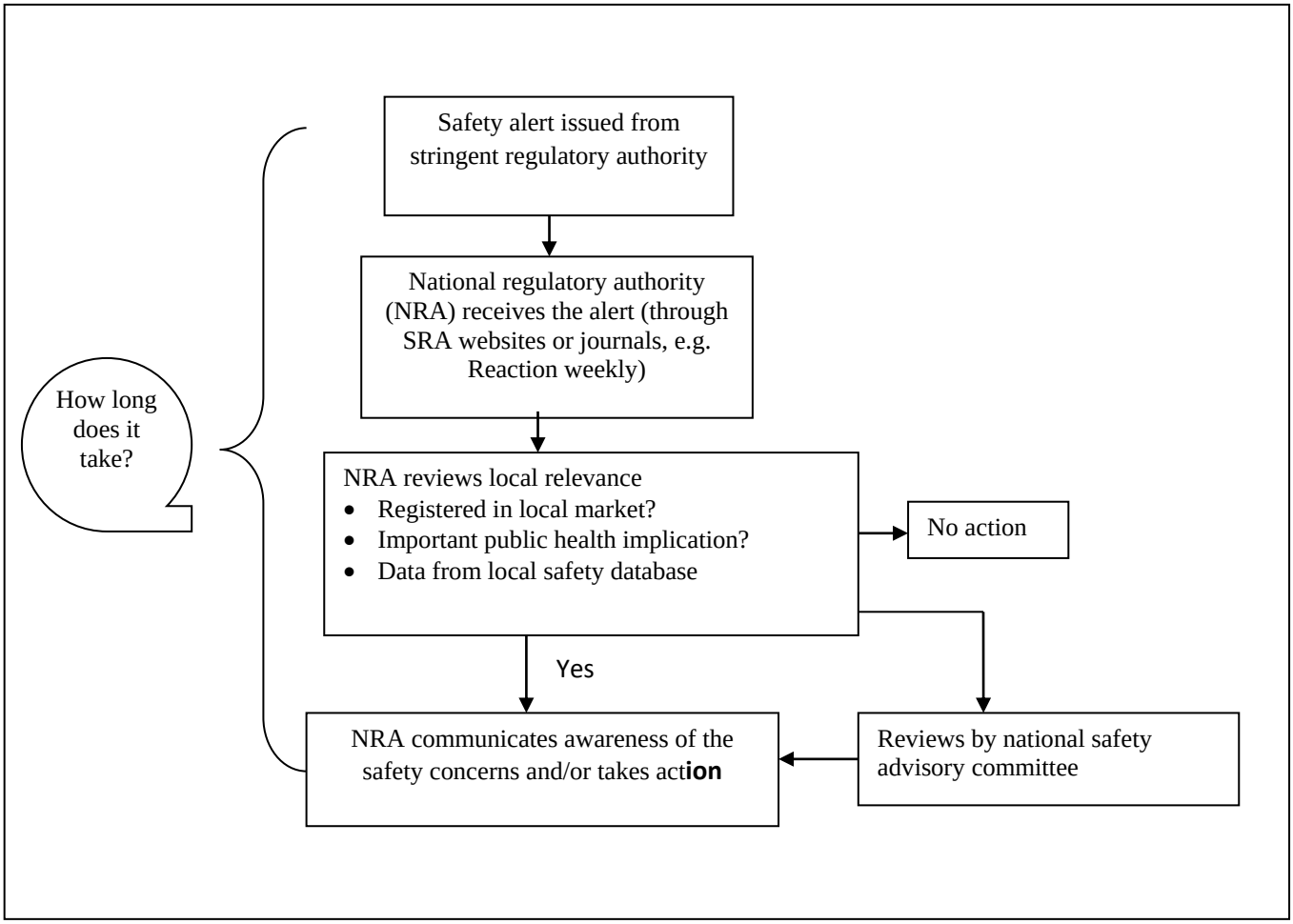

Figure 1.6: Proposed process for national regulatory authorities to react to emerging safety issues (Nwokike, Kabore, & Stergachis, 2014).

The main goal of regulatory pharmacovigilance can be précised as follows-

1. Keep the authorized drug under supervision clinically for long term tosspot the undesired effects of drug that has not been included in the safety profile
2. Computation of risk benefit ratio of the marketed drug to take action ensuring patient's safety
3. Providing all the drug related information to the patient to elevate the safe and effective use of drug

4. Supervise the significance of action that has been taken

1.9 Pharmacogenetics&Pharmacovigilance:

Pharmacogenetics add up a new hope for preventing and managing ADR and make a safe use of drug for every patient considering the slight changes in individuals physiology or body mechanisms. How an inherited characteristic can influence the effect of drug or can lead to death of a patient after using a specific drug can explain by pharmacogenetics. Human body is completely controlled by the gene and scientists have found connections between the ADME of a drug in one patient and his/her genetic pattern.

In this advance world scientists turns the fiction into reality, the disease are trying to be treated for the lifelong and treatment has developed in genetic level. Though the concept of pharmacogenetics is like under construction means it's till now experimental, it creates an opportunity to avoid any kind of ADR. Now-a-days numerous effort has been done to collaborate the genomic database with clinical, social and laboratory data(Farahani & Levine, 2006).

If the ADME of a drug in the body can predict before using the drug, it may be possible to control the ADE of a drug and maintain patient safety which is the first objective of a pharmacist and other health care professionals.

Studies shows factors related to genetics can dominate the therapeutic effect of a drug-

- Genetic polymorphism: can altered metabolism of a drug. Changes in drug metabolism can shift the concentration of a drug in the body can lead to a drug its active, inactive or toxic level.
- Genetic variants: can raise undesired drug effect .For example, hemolysis in glucose-6-phosphate dehydrogenase deficiency).
- Genetic variation in a drug target: can produce the alteration in clinical response and frequency of side effects. Such as- alteration of beta adrenergic receptor changes the response to beta agonists in asthma patients (Meyer).

Now, researchers are trying to developing pharmacogenetics based individual drug dosing system so ADE can be completely removed in using drug to treat a specific disease.

1.10 Rationale of the project:

In present numerous number of medicines have been discovered and developed to advance the health care system and reduce the mortality rate. However, medicines that are used to treat disease sometimes cause serious ADRs even leading to dealth. Now-a-days, the managing of these ADR become a global concern to ensure the public health. The rationale of this project is to spot out the significance of post-authorisation study in pharmacovigilance and reporting ADR and address the aspects contribute to develop the pharmacovigilance system globally.

1.11 Aim of the project :

The aim of my project is to show the recent development of pharmacovigilance in terms of post-authorisation study globally.

1.12 Objectives of the project:

The objective of the paper is to explore the articles published about the topic related to pharmacovigilance and find out the correlation between regulatory actions, effective reporting and pharmacogenetics in the advancement of post authorisation study and pharmacovigilance program.

Chapter Two: Methodology

2.1 Study design :

The study has been designed to address the answer of the following questions

- Are clinical trials and post authorization studies of pharmacovigilace enough to create a complete safety profile for a drug?
- How regulatory actions can facilitates the pharmacovigilace practice and ensure a safe use of drug?
- How can the effective reporting of ADR and signal minimize the occurrence of ADR?
- What is the role and development of pharmacogenetics for advancing the pharmavigilance practice?

The main focus of this paper is to reveal the answer of these questions.

2.2 Literature Search :

An electronic search has been conducted to collect journals and articles related to the questions.The publications from which the journals and research and review articles have been assembled are given below -

1. Pudmed
2. Medline
3. Hinary
4. Elsevier
5. Nature
6. Wiley
7. Plos One
8. Biomedcentral (BMC)
9. Google Scholar
10. British journal of clinical pharmacology
11. Journal of nursing management

12. Dovepress
13. Future medicine
14. Biomed research international
15. Springer Link
16. JMIR Public Health and Surveillance

The key words have been used to accumulate the exact data are-

1. Adverse Drug Reaction
2. Pharmacovigilance system
3. Post-authorisation study of pharmacovigilance
4. ADR reporting
5. Pharmacogenetics in pharmacovigilance
6. Regulatory action in pharmacovigilance
7. Management of ADR
8. Complete safety profile of drug
9. Development of pharmacogenetics to control ADR etc.

All the journals and research papers have been collected from the renowned sources and data has been extracted and included in the papers according to the study question to find the answer.

Chapter Three: Result & Discussion

3.1 Safety profile of drug:

The management of ADRs is the current challenge for the scientists and researchers. The main focus is to identify the pattern or cause to predict the ADR before it's happen. Analyzing the previous database or cases of ADE, it may be possible to take precaution and manage ADR within tolerable level.

Pharmacovigilance study can create a complete profile of drug which may include all possible ADR and cases or condition leading to the ADE. There have been many lists of drugs which have been found injurious during post-authorization study and have been withdrawn from the market.

Table 3.1: List of anti-obesity drugs withdrawn from the market because of adverse drug reactions (I. J. Onakpoya, C. J. Heneghan, & J. K. Aronson, 2016).

Medicinal product	Launch date	Year of first ADR report	Year first withdrawn	Primary reason for withdraw
Amphetamine	1939	1957	1973	Drug abuse and dependence
Benfluorex	1976	2003	2009	Cardiotoxicity
Cloforex	1965	1967	1967	Cardiotoxicity
Dexfenfluramine	1995	1995	1997	Cardiotoxicity
Fenfluramine	1973	1981	1997	Cardiotoxicity
Mazindol	1970	1980	1987	Drug abuse, psychiatric (interaction with lithium)

Mefenorex (methylphenethylamine)	1966	1995	1999	Drug abuse, drug dependence
Phentermine	1959	1964	1981	Drug abuse

From the table it has been noticed that most of the anti-obesity drug has been withdrawn from market due to the similar ADR which are cardio toxicity, drug abuse and psychiatric issue. Therefore, these are the common ADRs for anti-obesity drug, inventors will try to invent new anti-obesity drug avoiding these ADRs.

Table 3.2 Drugs withdrawn in the UK by the marketing authorisation holder or suspended or revoke by the Licensing Authority, 1975-2010 (Andrews & Moore, 2014).

Drug substance	Year action taken	Major safety concern
Polidexide	1975	Safety concerns because of impurities
Benoxaprofen	1982	Hepatotoxicity, serious skin reactions
Zomepirac	1983	Anaphylaxis
Fenclofenac	1984	Serious skin reactions, multisystem toxicity
Perhexiline	1985	Hepatotoxicity, neurotoxicity
Nomidensine	1986	Hemolytic anemia
Dilevalol	1986	Hepatotoxicity
Triazolam	1991	Psychiatric reactions
Pemoline	1997	Hepatotoxicity
Mibefradil	1997	Drug interactions
Raxar	1999	QT interval prolongation
Carisoprodol	2007	abuse potential
Rimonabant	2008	Depression, Suicide
Efalizumab	2009	Progressive Multifocal Leukoencephalopathy
Rosiglitazone	2010	Increased cardiovascular event risk

In the above table there has been a list of drugs withdrawn from UK market due to some major safety concern.

Therefore, from the above table 3.1 & 3.2, it has been clear that authorized drug doesn't always indicate the complete safety of the drug, post-authorisation observation and study is necessary to

create the complete safety profile of the drug. The post-authorisation studies are able to explain all the indications, contraindications and safety issues related to the medicinal product.

3.2 Regulation on pharmacovigilance :

Government involvement and regulatory actions can accelerate the pharmacovigilance programme. It can vary country to country's perspective and types of government organizational pattern etc. Therefore, standardization of the pharmacovigilance system helps to maintain the quality and realiblity of the database and result of the research all over the world. The Brazilian constitution's commitment to its citizens in the health sector consists of rational use of drugs,maintain the quality of drugs and price control of the essential drug (Moscou, Kohler, & MaGahan, 2016). United States and European Union establish laws for the approval of biological products as these products are prone to induce immunogenecity and can cause severe ADR, even dealth (Giezen et al., 2008).

Table 3.3: Post-marketing withdrawal of medicinal products because of adverse drug reactions in different continents (Igho J. Onakpoya, Carl J. Heneghan, & Jeffrey K. Aronson, 2016).

Continent	No. of countries	Total population (millions)	No. of withdraw products	Rate of withdrawals million population	Rate of withdrawal/ country
Africa	54	1111	63	0.06	1.17
Asia	46	4427	150	0.03	3.26
Australasia & Oceania	11	30	32	1.07	2.91
Europe	50	742.5	309	0.42	6.18
N.America	23	528.7	134	0.25	5.83
S. America	12	387.5	65	0.17	5.42

From the table it has been found that rate of drug withdrawn per country is highest in Europe continent and lowest in Africa. Therefore, the regulatory authorities in Europe are more concren

about their patient safety and their regulations are more strong than the other continents. However, Various low and middle-income countries take regualtory actions to the safety alerts while Bangladesh plays quite silent role to take initiatives in the establishment of pharmacovigilance system. In the following, the table shows how 10 low and middle –income coutries take regulatory steps against the risk associated with the drug rosiglitazone when identified by FDA and EMA-

Table 3.4: Regulatory actions with rosiglitazone by selected low- and middle-income countries (Nwokike, Kabore, & Stergachis, 2014).

Country	**Suspension**	**Enforcement**	**Communication Method**	**Date of Action**	**Lag Time, d**
Ghana	Yes		Safety alert	Nov 29, 2010	67
Kenya	Yes		Safety alert (e-shot)	Oct 13, 2010	20
Namibia	Yes		Safety alert	Nov 10, 2010	48
Nigeria		Yes	Safety alert + press release	Oct 9, 2010	16
Tanzania	Yes		Not Available	Nov 5,2010	43
Uganda	Yes		Not Available	Not Available	N/A
Senegal	Yes		Safety alert	Oct 12, 2010	19
South Africa	Yes		Safety alert	Jul 5, 2011	285
India	Yes		Safety alert	Oct 7, 2010	14
Indonesia	Yes		Safety alert	Sep 24, 2010	1

From the Table 3.4, it can be assumed that esblishment of laws and its implement does not always depend on the financial status of the countries. Some other factors may influene the regulatory actions like educational status, governmental structure and development of health care facilities of the country.

The Government awareness for managing ADR and creating pharmacovigilance system varies from country to country. All over the world USA and Europe have their strict rules and regulations to ensure the safe use of medicine and protect their patient's right in the healthcare system. Some other coutries also play an examplary role in advancing their healthcare system for the citizens. For example, one research show the pharmacovigilance program in Brazil and how their government and regulatory authorities work for providing healthcare opportunities to all its citizens and maintain patient's safety.

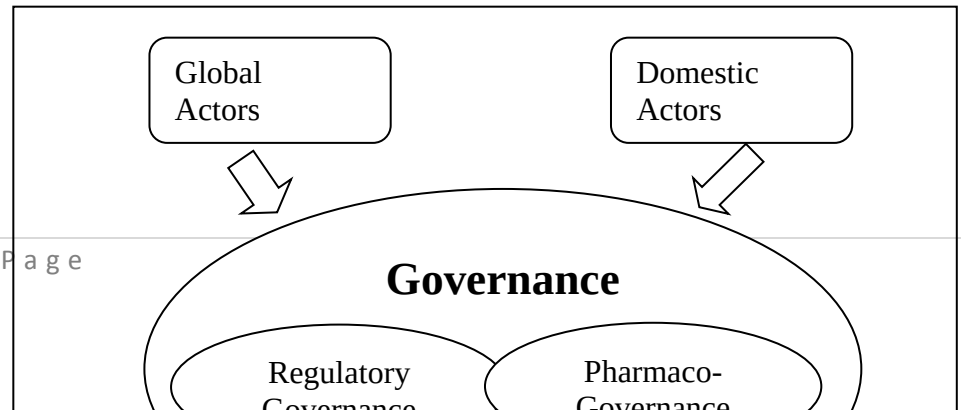

Figure 3.1: Factors influencing pharmacovigilance in Brazil

Figure 3.1 shows global and domestic actor of health sector collaborate with the govarnance system and construct regulatory and pharmaco-governance, finally teamed up with pharmacovigilance system to confirm the health rights of citizens. Here, ‘Pharmacogovernance can be defined as the manner in which governing structures, policy instrument and institutional authority (ability to act, implement and enforce norms, policies and processes) are managed to promote societal interests for patient safety and protection from ADE.

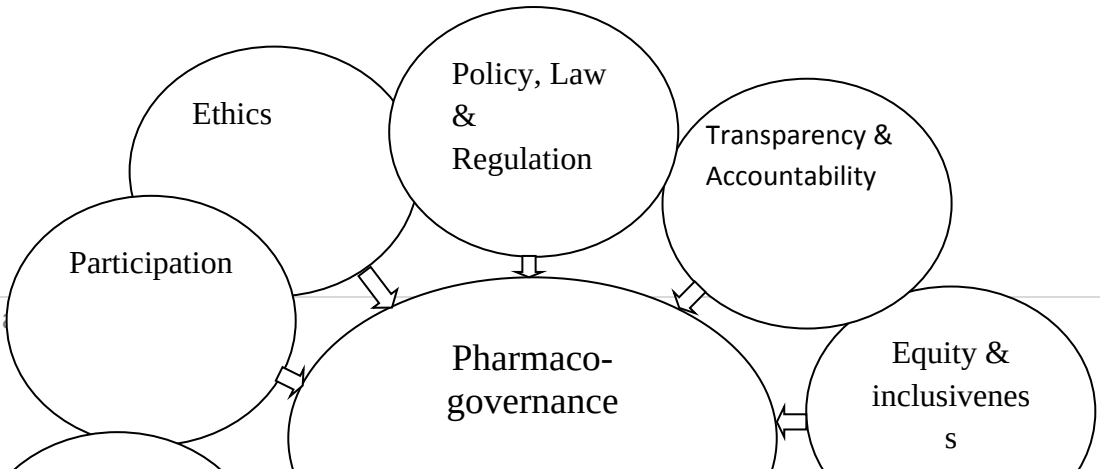

Figure 3.2: Pharmacovigilance framework

The figures shows that to run proper pharmacovigilance program the country must have well defined policy, law and regulation. Pharmacogovernance system must share its information and decision to the citizens and also responsible for the results of their act. In the pharmacovigilace system there must have some space for the participation of all citizens in case of policy making. Enough economic and social resoures must be provided to national pharmacovigilance system so that all citizens get access to safe medicines. If any actions take timely that will be considered as efficient and if the actions beneffit the patient that can be termed as effective. There must have a definite procedure to create a communication bridge among regulatory authorities, health care professionals, patient, citizens, pharmacovigilance authorities in favor of patient safety. The system must maintain the moral principles to protect the civilians right to safe medicines and health. The system must have the capability to act instantly to locate the safety hazards and enact policy and regulations. Lastly, there must have been a network within global and domestic actors to organize the actions designed to reinforce the pharmacovigilance system (Moscou et al., 2016).

From the figure 3.1 & 3.2, it can be comprehned that interrelation between government and pharmacovigilance method strengthen the pharmacovigilance system.

As biological products are more vulnarable to cause ADR and severe immune response in the body , USA and European Union have more firm control over these products. How USA and European Union control the prescription and use of biologicals are given below-

Table 3.5: Biologicals With a Direct Healthcare Professional Communication (DHPC) in the European Union (Giezen et al., 2008).

Class of Biological	**Active Substance**	**Warning**	**Time to DHPC, y**
Antibodies	Alemtuzumab	Cases of death related to infection	6.6
Cytokines	Anakinra	Serious infection and neutropenia in combination with etanercept	0.9
Enzymes	Lepirudin	Fatal anaphylactic reactions	5.6
Growth Factors	Diboterminalfa	Postoperative edema at application site implant site fluid collections	1.9 4.5
Hormones	Insulin human inhalation powder	Primary lung carcinoma	2.4
Others/Various	Botulinum toxin	Muscle weakness, dysphagia, aspiration	6.3
Receptors	Etanercept	Blood dyscrasia (pancytopenia, aplastic anemia, anemia) Serious infections and neutropenia in combination with kineret	0.7 3.0

Table 3.6: Biologicals With a Dear Healthcare Professional Letter (DHPL) in the United States (Giezen et al., 2008).

Class of Biological	**Active Substance**	**Warning**	**Time to DHPC, y**
Antibodies	Alemtuzumab	Serious infection in combination with anakinra, hypersensitivity, reactions,	1.8

		hematologic events	
Cytokines	Denileukin Diftitox	Visual loss	7.1
Enzymes	Eptacog Alfa	Thrombotic and thromboembolic adverse events	6.7
Growth Factors	Becaplermin	Increased risk of mortality secondary to malignancy	10.5
Hormones	Insulin Human inhalation Powder	Primary lung malignancy	2.2
Interferon's	Interferon beta-1a	Antibody formation hepatic injury	5.8 7.7

From the table 3.5 & 3.6 it has been found that United States and European Union maintain strong regulation against safety alerts. Depending on the severity of the risk factors it takes times and more intensive observation and research for approving a medicine.

3.3 ADR reportig :

Pharmacovigilance system need proper reporting of ADR to maintain a database and doing research with them to find out the solution or management pattern of ADR and decrease the severity and mortality due to ADR. Reporting ADR is the first and foremost step of pharmacovigilance, so many studies have been done to determine the factors that can accelerate the ADR reporting and how encourages the healthcare professionals for reporting ADR.

Table 3.7: Demography details and characteristic features of the respondents (Santosh, Tragulpiankit, Gorsanan, & Edwards, 2013).

(A)

Category	**Sub-category**	**Number(%)**
	Male	128 (38.4)

Gender	Female	201 (60.4)
	Data Missing	4 (1.2)
Age (years)	Up to 20	9(2.7)
	21-30	221 (66.4)
	31-40	69 (20.7)
	41-50	19 (57)
	51-60	3 (0.9)
	above 60	6 (1.8)
	Mean	29.5
	Minimum	19
	Maximum	72
	Data Missing	6 (1.8)
Professional Qualification	Doctor	162 (48.6)
	Nurse	135 (40.5)
	Pharmacist	32. (9.6)
	Data missing	4 (1.2)

(B)

Category	**Sub-category**	**Number(%)**
Doctor	MD/MS	70 (21.0)
	MBBS	86 (25.8)
	MDS	3 (0.9)

	BDS	2 (0.6)
Nurse	MN	2 (0.6)
	BN	36 (10.8)
	PCL	97 (29.1)
Pharmacist	Phd and Master	9 (2.7)
	B.pharm	6 (1.8)
	PCL/Diploma	17 (5.1)

Above table shows the percentage of ADE respondents corresponding with the different criteria. Adverse drug reactions reported by consumers for nervous system medications in Europe 2007 to 2011 has been shown in the following –

Table 3.8: Fatal consumer cases reported for nervous system medications in Europe, 2007 to 2011 (Aagaard & Hansen, 2013).

Case No	**Medicine (s)**	**Adverse drug reaction (s)**	**Sex (M/F)**	**Age**
1	Diamorphine	Sudden death	F	18+
2	Morphine	Cerebrovascular accident		
3	Apomorphine	Pneumonia	M	NA
4	Apomorphine	Intestinal haemorrhage	M	NA
		Pneumonia aspiration		
5	Apomorphine	Anaemia	F	18+
		Haematocrit decreased		
		Red blood cell sedimentation rate		

		increased		
6	Apomorphine	Death	F	18+
7	Apomorphine	Death	F	NA
8	Apomorphine	Death	F	18+
9	Carbidopa/levodopa	Death	M	18+
10	Clozapine	Cardiac failure	F	18+
11	Duloxetine	Deafness	F	18+
		Abasia		
		Urinary tract infection		
		Septic shock		
		Urosepsis		
		Hyponatremia		
		Neoplasm malignant		
		Aphasia		
		Urinary incontinence		
		Renal failure		
12	Trimipramine	Asthenia	M	18+
		Depressed level of consciousness/sedation		
		Tachyphrenia		
		Completed suicide		

		Dependence		
		Indifference		

From the data given in the table, it can be assumed that ADR occurence due to the use of nervous system medicines mostly found in females than males.

Analyzing the all ADR cases occuring worldwide scientists have been found some drugs which are mostly related to ADR. The list of drug classes and individual drugs most commonly associated with ADRs are given below-

1. Antibiotics: Cephalexin
   Cefalotin
   Cefazolin
   Cefepime
   Ceftriaxone
   Imipenem
   Oxacilline
   Rifampicin
   Vancomycin
2. Analgesics: Metamizole
   Paracetamol
3. Antipsychotics: Chlorpromazine
   Olanzapine
   Risperidone
4. Opioids: Fentanyl

		Tramadol
5.	Benzodiazepine:	Diazepam
		Midazolam
6.	ACE inhibitors :	Captopril
		Enalapril
7.	Antiarrhythmic:	Amiodarone
8.	Local anesthetic:	Bupivacaine
9.	Anticonvulsant:	Phenytoin
10.	Beta-Blocker:	Carvedilol
11.	Antiemetic:	Metoclopramide
12.	H_2 receptor antagonist:	Ranitidine
13.	Antidiuretic:	Furosemide

(Lobo, Pinheiro, Castro, Momenté, & Pranchevicius, 2013).

From the above listed drug the percentage of ADR is relaively low, so these ADR seems to be manageable and controlled by proper observation and monitoring and possibily can avoid by indetifying the cause of ADR.

Table 3.9: Characteristics of patients whose deaths were considered ADR-related, vs. patients whose deaths were not considered ADR-related (Mouton et al., 2015).

	All deaths	ADR-related deaths	Other deaths
All patients: n	357	56	301

Females: n (%)	184	30	154
Age (years): median (IQR)	53	52.5	53
Known HIV infected (%)	135	31	104
On treatment for TB (%)	55	14	41
Number of drugs exposed to: median (IQR)	7	9	7
Modified charlson co-morbidity index score: median (IQR)	2	2	2
Time from admission to death (days): median (IQR)	5	6.5	5
HIV-infected patients only:	135	31	104
Females:	61	15	46
Age (years): median (IQR)	37	37	37
CD4-count (cells mm^{-3}): median (IQR)	52	126	41
On ART (%)	66	20	46
On treatment for TB (%)	45	12	33
Number of drugs exposed to: median (IQR)	9	9	9
Modified Charlsonco-morbidity score: median (IQR)	0	2	0
Time from admission to death (days): median (IQR)	5	4	5.5

Table 3.9 shows the result has been found after surveying four hospitals in South Africa trying to find out the mortality rate of adult inpatient due to ADR. Here, the percentage of dealth because of ADR is relatively low than the death due to other reasons.

3.4 Role of Pharmacogenetics :

Table3.10: Associations between genetic variants involved in pharmacokinetics and pharmacodynamics and their related ADRs (Su, Chung, & Hung, 2014).

Genetic Variants	ADR	Drug
ABCB1 (rs1045642)	Nephrotoxicity	Cyclosporine
ABCC4 (rs9561778)	Leukopenia/toxicity	Cyclophosphamide
CYP2C19*2	Decreased platelet responsiveness	Clopidogrel
CYP2C19*2, CYP2C19*17	Altered pharmacokinetics	Citalopram
CYP2D*2	Opioid intoxication	Codeine
Polymorphic NAT2	Toxicity	Hydralazine, sulfasalazine
SLC22A2 (rs316019)	Reduced nephrotoxicity	Cisplatine
CLCO1B1 (rs4149056)	Myopathy	Simvastatin
TPMT*2,TPMT*3A, TPMT*3C	Hematologic Toxicity	Mercaptopurine, azathioprine
UGT1A1*28	Toxicity	Irinotecan

Table 3.10 shows how genetic variants lead to the severe ADR for specific drug

Table 3.11: Clinically important genetic polymorphisms of drug metabolism that influence drug response (Meyer,2000)

Enzyme	Frequency of polymorphism	Drug	Drug effect
CYP2C9	14-28% (heterozygotes) 02-1% (homozygotes)	Warfarin Tolbutamide Phenytoin Glipizide Losartan	Haemorrhage Hypoglycaemia Phenytoin toxicity Hypoglycaemia Decreased antihypertensive effect
CYP2D6	5-10% (poor metabolisers) 1-10% (ultra-rapid metabolisers)	Antiarrhythmics Antidepressants Antipsychotics Opioids β-adrenoceptor antagonists	Proarrhythmic and other toxic effects Toxicity in poor metabolisers, inefficacy in ultra-rapid metabolisers Tardive dyskinesia Inefficacy of codeine as analgesic, narcotic side effects dependence Increased β-blockade
CYP2C19	3-6% (whites) 8-23% (Asians)	Omeprazole Diazepam	Higher cure rates when given with clarithromycin Prolonged sedation
Dihydropyrimidine dehydrogenase	0.1%	Fluorouracil	Neurotoxicity myelotoxicity
Plasma pseudo-cholinesterase	1.5%	Succinylcholine	Prolonged apnoea
N-acetyltransferase	40—70% (whites) 10—20%	Sulfonamides Amonafide	Hypersensitivity Myelotoxicity (rapid acetylators)

	(Asians)	Procainamide Hydralazine Isoniazid	Drug-induced lupus erythematosus
Thiopurine methyltransferase	0.3%	Mercaptopurine Thioguanine azathioprine	Myelotoxicity
UDP-glucuronosyltransferase	10-15%	Irinotecan	Diarrhoea, myelosuppression

Genetic polymorhism can determine the ADME and toxicity of a drug, therefore helps to predict the ADE to analyze the patient genetic history and maping. Such as, the metabolism of some tricyclic antidepressant drugs depend on a specific enzyme CYP2C9. In this case, two types of patient may suffer from the ADR. They are classified as poor metaboliser and rapid metaboliser. Patients having poor or rapid metaboliser face ADE in the recomanded dose needed for the treatment of actual disease.

Chapter Four: Conclusion

Though adverse drug reaction beacoming a major concern for health care professionals because of its severity, researchers finally come up with the solution by creating an organised method named pharmacovigilance system. In this paper we tried to search the answer of four question related to the post-authorisation study of pharmacovigilance system. After analyzing the data collected from different journals it has been confirmed post-authorisation study is the main core to create an absolute drug safety profile. Assimilation of regulatory authorities of medicine system and government can restore the faith on medicine by diminishing the risk of ADR. Proper laws and implimentation of them for the approval of medicine to market lunch and prescription and documentation of a single safety related reports ensure the patient safety. Adequate ADR reporting and signal detection is crucial step to constitute a pharmacovigilance database to from where researchers obtain sufficient input to conduct studies and generate the new factors that control the ADR reoccurance and lessen the uncertainity. Futhermore, the signal detection an facilitate the action of regulatory authorities to decide that whether the ADR is serious or not and take steps accordingly. Pharmacogenetics term in the pharmacovigilance system is the advance technology for detecting ADR before it occurs and prescribe and maintain the use of drug to be safe for patient by analyzing the genetic makeup of the patient and determine the genetic varients responsible for causing ADR.

Reference

Aagaard, L., & Hansen, E. H. (2013). Adverse drug reactions reported by consumers for nervous system medications in Europe 2007 to 2011. *BMC Pharmacol Toxicol, 14*, 30-30. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3685574/ doi:10.1186/2050-6511-14-30

Alhawassi, T. M., Krass, I., Bajorek, B. V., & Pont, L. G. (2014). A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clinical Interventions in Aging, 9*, 2079-2086. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4257024/ doi:10.2147/CIA.S71178

Andrews, E. B., & Moore, N. (2014). *Mann's pharmacovigilance* Retrieved from http://public.eblib.com/choice/publicfullrecord.aspx?p=1662669

Black, C., Tagiyeva-Milne, N., Helms, P., & Moir, D. (2015). Pharmacovigilance in children: detecting adverse drug reactions in routine electronic healthcare records. A systematic review. *Br J Clin Pharmacol, 80*(4), 844-854. Retrieved from http://onlinelibrary.wiley.com/store/10.1111/bcp.12645/asset/bcp12645.pdf?v=1&t=irxl95tv&s=6e603c370e4e8a18d5f2992c45a573beed6cd194 doi:10.1111/bcp.12645

Blass, B. E. (2015). *Chapter 1 - Drug Discovery and Development: An Overview of Modern Methods and PrinciplesBasic Principles of Drug Discovery and Development* (pp. 1-34).Retrieved from http://www.sciencedirect.com/science/article/pii/B9780124115088000013 doi:https://doi.org/10.1016/B978-0-12-411508-8.00001-3

Conforti, A., Opri, S., D'Incau, P., Sottosanti, L., Moretti, U., Ferrazin, F., & Leone, R. (2012). Adverse drug reaction reporting by nurses: analysis of Italian pharmacovigilance database. *Pharmacoepidemiol Drug Saf, 21*(6), 597-602. doi:10.1002/pds.3225

Farahani, P., & Levine, M. (2006). Pharmacovigilance in a genomic era. *The pharmacogenomics journal, 6*(3), 158.

Giezen, T. J., Mantel-Teeuwisse, A. K., Straus, S. M., Schellekens, H., Leufkens, H. M., & Egberts, A. G. (2008). Safety-related regulatory actions for biologicals approved in the united states and the european union. *JAMA, 300*(16), 1887-1896. Retrieved from http://dx.doi.org/10.1001/jama.300.16.1887 doi:10.1001/jama.300.16.1887

Hakkarainen, K. M., Hedna, K., Petzold, M., & Hagg, S. (2012). Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions--a meta-analysis. *PLoS ONE, 7*(3), e33236. doi:10.1371/journal.pone.0033236

Hassan, W. E. (1986). *Hospital pharmacy [by] William E. Hassan, Jr*

Lobo, M. G. A. d. A., Pinheiro, S. M. B., Castro, J. G. D., Momenté, V. G., & Pranchevicius, M.-C. S. (2013). Adverse drug reaction monitoring: support for pharmacovigilance at a tertiary care hospital in Northern Brazil. *BMC Pharmacol Toxicol, 14*, 5-5. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3554560/ doi:10.1186/2050-6511-14-5

Lorimer, S., Cox, A., & Langford, N. J. (2012). A patient's perspective: the impact of adverse drug reactions on patients and their views on reporting. *J Clin Pharm Ther, 37*(2), 148-152. doi:10.1111/j.1365-2710.2011.01258.x

Meyer, U. A. Pharmacogenetics and adverse drug reactions. *The Lancet, 356*(9242), 1667-1671. Retrieved from http://dx.doi.org/10.1016/S0140-6736(00)03167-6 doi:10.1016/S0140-6736(00)03167-6

Mirbaha, F., Shalviri, G., Yazdizadeh, B., Gholami, K., & Majdzadeh, R. (2015). Perceived barriers to reporting adverse drug events in hospitals: a qualitative study using theoretical domains framework approach. *Implementation Science, 10*(1), 110. doi:10.1186/s13012-015-0302-5

Montastruc, J.-L., Lapeyre-Mestre, M., Bagheri, H., & Fooladi, A. (2002). Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. *Fundamental & Clinical Pharmacology, 16*(5), 343-346. Retrieved from http://dx.doi.org/10.1046/j.1472-8206.2002.00100.x doi:10.1046/j.1472-8206.2002.00100.x

Moscou, K., Kohler, J. C., & MaGahan, A. (2016). Governance and pharmacovigilance in Brazil: a scoping review. *Journal of Pharmaceutical Policy and Practice, 9*(1), 3. Retrieved from http://dx.doi.org/10.1186/s40545-016-0053-y doi:10.1186/s40545-016-0053-y

Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., . . . Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. *Br J Clin Pharmacol, 80*(4), 818-

826. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=aph&AN=109967394&site=ehost-live

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594724/pdf/bcp0080-0818.pdf doi:10.1111/bcp.12567

Neutel, C. I. (2009). *An Introduction to Pharmacovigilance by Patrick Waller* Vol. 20. *Annals of Epidemiology* (pp. 965-966). Retrieved from http://dx.doi.org/10.1016/j.annepidem.2010.09.001 doi:10.1016/j.annepidem.2010.09.001

Nwokike, J., Kabore, L., & Stergachis, A. (2014). Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone. *Therapeutic Innovation & Regulatory Science*, *49*(2), 279-283. Retrieved from http://dx.doi.org/10.1177/2168479014551644 doi:10.1177/2168479014551644

Onakpoya, I. J., Heneghan, C. J., & Aronson, J. K. (2016). Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Medicine*, *14*, 10-10. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=26843061&site=ehost-live

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740994/pdf/12916_2016_Article_553.pdf doi:10.1186/s12916-016-0553-2

Onakpoya, I. J., Heneghan, C. J., & Aronson, J. K. (2016). Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. *BMC Med*, *14*(1), 191. doi:10.1186/s12916-016-0735-y

Qing-ping, S., Xiao-dong, J., Feng, D., Yan, L., Mei-ling, Y., Jin-xiu, Z., & Shu-qiang, Z. (2014). Consequences, measurement, and evaluation of the costs associated with adverse drug reactions among hospitalized patients in China. *BMC Health Services Research*, *14*, 73-73. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=24533894&site=ehost-live

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3931293/pdf/1472-6963-14-73.pdf doi:10.1186/1472-6963-14-73

Rydberg, D. M., Holm, L., Engqvist, I., Fryckstedt, J., Lindh, J. D., Stiller, C.-O., & Asker-Hagelberg, C. (2016). Adverse Drug Reactions in a Tertiary Care Emergency Medicine Ward - Prevalence, Preventability and Reporting. *PLoS ONE, 11*(9), 1-14. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=aph&AN=118050739&site=ehost-live

http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0162948&type=printable doi:10.1371/journal.pone.0162948

Santosh, K. C., Tragulpiankit, P., Gorsanan, S., & Edwards, I. R. (2013). Attitudes among healthcare professionals to the reporting of adverse drug reactions in Nepal. *BMC Pharmacol Toxicol, 14*, 16. doi:10.1186/2050-6511-14-16

Sharrar, R. G., & Dieck, G. S. (2013). Monitoring product safety in the postmarketing environment. *Ther Adv Drug Saf, 4*(5), 211-219. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4125313/pdf/10.1177_2042098613490780.pdf doi:10.1177/2042098613490780

Su, S.-C., Chung, W.-H., & Hung, S.-I. (2014). Digging up the human genome: current progress in deciphering adverse drug reactions. *Biomed Research International, 2014*, 824343-824343. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=24734245&site=ehost-live

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3966344/pdf/BMRI2014-824343.pdf doi:10.1155/2014/824343

Conforti, A., Costantini, D., Zanetti, F., Moretti, U., Grezzana, M., & Leone, R. (2012). Adverse drug reactions in older patients: an Italian observational prospective hospital study. *Drug, Healthcare and Patient Safety, 4*, 75-80. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413040/ doi:10.2147/DHPS.S29287

Franceschi, M., Scarcelli, C., Niro, V., Seripa, D., Pazienza, A. M., Pepe, G., . . .Pilotto, A. (2008). Prevalence, clinical features and avoidability of adverse drug reactions as cause

of admission to a geriatric unit: a prospective study of 1756 patients. *Drug Saf, 31*(6), 545-556.

De Paepe, P., Petrovic, M., Outtier, L., Van Maele, G., &Buylaert, W. (2013). Drug interactions and adverse drug reactions in the older patients admitted to the emergency department. *ActaClinBelg, 68*(1), 15-21.doi:10.2143/acb.68.1.2062714

Hellden, A., Bergman, U., von Euler, M., Hentschke, M., Odar-Cederlof, I., &Ohlen, G. (2009). Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. *Drugs Aging, 26*(7), 595-606. doi:10.2165/11315790-000000000-00000

Kojima, T., Akishita, M., Kameyama, Y., Yamaguchi, K., Yamamoto, H., Eto, M., &Ouchi, Y. (2012). High risk of adverse drug reactions in elderly patients taking six or more drugs: analysis of inpatient database. *GeriatrGerontolInt, 12*(4), 761-762. Retrieved from doi:10.1111/j.1447-0594.2012.00868.x

Laroche, M.-L., Charmes, J.-P., Nouaille, Y., Picard, N., & Merle, L. (2007). Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *Br J ClinPharmacol, 63*(2), 177-186. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2000580/ doi:10.1111/j.1365-2125.2006.02831.x

Lattanzio, F., Laino, I., Pedone, C., Corica, F., Maltese, G., Salerno, G., . . .Incalzi, R. A. (2012). Geriatric conditions and adverse drug reactions in elderly hospitalized patients. *J Am Med DirAssoc, 13*(2), 96-99. Retrieved from doi:10.1016/j.jamda.2011.04.006

Sikdar, K. C., Dowden, J., Alaghehbandan, R., MacDonald, D., Peter, P., &Gadag, V. (2012). Adverse drug reactions in elderly hospitalized patients: a 12-year population-based retrospective cohort study. *Ann Pharmacother, 46*(7-8), 960-971. doi:10.1345/aph.1Q529

Olivier, P., Bertrand, L., Tubery, M., Lauque, D., Montastruc, J. L., &Lapeyre-Mestre, M. (2009). Hospitalizations because of adverse drug reactions in elderly patients admitted through the emergency department: a prospective survey. *Drugs Aging, 26*(6), 475-482. doi:10.2165/00002512-200926060-00004

Ma, J., Wang, Y., Gao, M., Meng, Q., & Liu, J. (2012). Adverse drug reactions as the cause of emergency department admission of patients aged 80 years and older.*Eur J Intern Med, 23*(6), e162-163. doi:10.1016/j.ejim.2012.05.004

Tangiisuran, B., Davies, J. G., Wright, J. E., &Rajkumar, C. (2012). Adverse drug reactions doi:10.2165/11632630-000000000-00000

O'Connor, M. N., Gallagher, P., Byrne, S., &O'Mahony, D. (2012). Adverse drug reactions in older patients during hospitalisation: are they predictable? *Age Ageing*, *41*(6), 771-776. doi:10.1093/ageing/afs046

Marcum, Z. A., Amuan, M. E., Hanlon, J. T., Aspinall, S. L., Handler, S. M., Ruby, C. M., & Pugh, M. J. (2012). Prevalence of unplanned hospitalizations caused by adverse drug reactions in older veterans.*J Am GeriatrSoc, 60*(1), 34-41. doi:10.1111/j.1532-5415.2011.03772.x