e - ISSN - 2249-7668
Print ISSN - 2249-7676

International Journal of
Pharmacology & Toxicology

www.ijpt.org

ADVERSE DRUG REACTION AND PHARMACOVIGILANCE- AN OVERVIEW

Vijayakumar Subash*

Associate Professor, Department of Pharmacy Practice, Vaagdevi College of Pharmacy, MGM Hospital, Warangal, Andhra Pradesh, India.

ABSTRACT

Adverse drug reaction by WHO "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of disease, or for the modification of physiological functions. Whereas, pharmacovigiliance as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. It warn's us and helps us in withdrawl of an offending pharmaceutical product. Our review article mainly focuses on the role of adverse drug reaction and pharmacovigiliance. We developed a search strategy to find publications about ADR and its management. So, we searched Science Direct, Medline and PubMed bibliographic databases using the key phrases causes of ADR, PV, and drugs under suspected unwanted reaction. Our review article suggests that, drug related problem in the community as well as in hospital increased in both developing and developed countries. Hence awareness should create among the public regarding proper usage of drugs and strengthen the pharmacovigilance program in every country.

Keywords: Drugs, Community, Hospital, Gender, Pharmacovigliance and India.

INTRODUCTION

Definition

Definition of adverse drug event by WHO "any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment". Whereas, definition of adverse drug reaction by WHO "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of disease, or for the modification of physiological functions". While, definition of lack of efficacy by WHO "an unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation". In addition to that definition of drug therapeutic failure by Hallas and coworkers "an absence of therapeutic response that could be linked causally either to a prescribed dose that was too low, to drug non-compliance, recent dose reduction/discontinuation, interaction or inadequate monitoring". Definition of drug therapeutic failure proposed in present paper "an adverse drug reaction in which the expected drug effects do not occur following a prescribed pharmacological treatment, including any clinical event that could be related to a low prescribed dose, to a recent dosage reduction/ discontinuation, or to non-compliance" [1-4]. Pharmacovigilance, an observational science about drug safety is the study of the drug related injuries [5]. The WHO defines pharmacovigilance (WHO 2002) as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. It helps us in warning or withdrawal of offending pharmaceutical product. The role of Pharmacovigilance can be divided into three main areas:

Corresponding Author:- **Subash Vijayakumar** Email:- vijayvijay66@yahoo.co.in

- To identify, quantify and document drug related problems.
- To contribute to reduce the risk of drug- related problems in health care systems.
- To increase knowledge and understanding of factors and mechanisms, which are responsible for drug related injuries.

The effect of a drug includes pharmacodynamic effects and side effects. Pharmacodynamic effects are the characteristic drug effects that are of interest for treating diseases; examples include an ability to decrease serum uric acid levels or to suppress inflammation. Pharmacodynamic effects are documented in animal studies then in Phase I and Phase II studies in humans and finally in Phase III clinical trials. Provided the dosage is adequate, they occur in all individuals. During drug development, the pharmacodynamic effect that is of greatest clinical relevance is identified. Phase III trials are designed to measure the selected pharmacodynamic effect (in examples above, efficacy against gout or analgesia). Their results are used by regulatory agencies to define the clinical indications of the drug. Side effects stem from documented pharmacological properties of the drug that exist in addition to the selected pharmacodynamic effect. Side effect may be beneficial or deleterious. For instance, H1 receptor antagonists prevent motion sickness, and the alpha adrenoceptor antagonist effect of imipramine antidepressants induces postural hypotension. A drug may also exert toxic effects, which occur in all individuals after exposure to an excessive dose. Toxicovigilance is a set of activities designed to detect and to investigate toxic effects. Pharmacovigilance in contrast, focuses on adverse drug reactions (ADRs), which are unwanted side effects. Pharmacovigilance studies are conducted not only on drugs (both old and new), but also on stable blood products (eg. Albumin, clotting factors, immunoglobulins and biological glues), contraceptives, contrast agents, vaccines and other products intened to promote human health. Unexpected Adverse Reaction: An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from the characteristics of the drug [5].

On the other hand, the term "Post-marketing surveillance (PMS) study" implies a scientifically rigorous study of a product that is approved for registration in a particular country, designed to produce reliable information about drug safety. It is not appropriate to apply the term to clinical trials of registered products or to studies designed primarily for marketing purposes regardless of the scientific validity of the study design. Wheras, Post-marketing surveillance studies are generally performed on the initiative of the sponsoring company, but may be suggested or requested by other parties. They should generally be designed to address a specific drug safety question or hypothesis (the latter often identified initially by voluntary reporting an adverse event (AE) is an untoward medical occurrence, which may or may not have a causal relationship with the treatment while medication errors, adverse drug events (ADEs) and adverse drug reactions (ADR) are related to the drug use [6].

Epidemiological Status of Adverse Drug Reaction

Several studies have found that risk of developing ADRs was more in females than males. Reasons suggested for this include differences in perception of ADRs, Pharmacology of ADRs, differences in pharmacokinetics such as volume of distribution, polypharmacy, and hormonal differences between men and women. The detection of adverse drug reaction has become increasingly significant because of introduction of a large number of potent toxic chemicals as drugs in the last two or three decades. WHO has intervened seriously in this matter and established an international adverse drug reactions monitoring centre at Uppsala, Sweden, which is collaborating with national monitoring centres in around 70 countries. In many countries, drug utilization studies have been performed by means of prescription databases, such as the Tayside database in Scotland the VAMP database in England, the Saskatchewan databases in USA, and the Pharma database in the Netherlands. Generally prescription databases have proved their value as powerful research tools for a multitude of pharmacoepidemiological studies, and studies comparing drug exposure according to different sources have demonstrated registered data as one of the most accurate sources of data. Prevention of adverse effects will be reduced by more skilful prescribing and this means that doctors among all the other claims on their time, must find time to understand drugs better, as well as to understand their patients and their diseases [7-9].

Surveillance Programs

Clinical pharmacists as well as all health care professionals should take an active role in monitoring, reporting, and trending ADR information. Some of the activities involved in a concurrent and ongoing ADR surveillance program at an institutional level include the following components

A. Clinical pharmacy departments should take the lead in the collection of information and should submit all reviews and reports to the pharmacy and therapeutics committees for review and evaluation.
1. Encourage all health care professionals to be involved in reporting
2. Monitor patients who are using high-risk agents
3. Review patients who have received "antidote"- type drugs
4. Notify prescribers of suspected ADRs and encourage through documentation of the description of the reaction as well as the outcome in patients medical records.
5. Report appropriately identified ADRs to the FDA

6. Develop the use of pharmacy computer systems to track ADRs

B. Evaluation of the causes of ADRs should be carried out. ADR report information should be used for educational purposes and identification of drug use and medication use processes to prevent further occurrences of such reactions. ADRs reporting information should be incorporated into institutional risk management programs.

Reporting to the FDA

Three of the five major centres at the FDA are involved with evaluating the safety and efficacy of drugs. The largest center is the center for Drug Evaluation and Research (CDER), which oversees both prescription and non-prescription – Over the Counter (OTC) – drugs. In 2002, CDER established the Adverse Event Reporting System (AERS), a computerized data base designed to support the FDA's Postmarketing safety program for drugs and therapeutic biologic products. Annually, the AERS receives about 470,000 reports of adverse experiences possibly associated with drugs. The center for Biological Evaluation and Research (CBER) ensures the safety and efficacy of blood products, vaccines, allergenics, biological therapeutics, gene therapy, medical devices and tests, xenotransplantation products, and banked human tissue and cellular products. The center for food safety and applied nutrition (CFSAN) established the CFSAN Adverse Events Reporting System (CAERS) in 2002. The CAERS provides a monitoring system to identify potentially serious problems secondary to non-FDA approved herbs, minerals, vitamins, dietary supplements, and other substances.

A. The national Vaccine Adverse Event Reporting System (VAERS) is co-administered by the FDA and the centers for disease control and prevention (CDC). More than 10 million vaccines are given to children and many million more doses to adults each year. Although vaccines protect many people from dangerous diseases, they do have the potential to cause adverse effects.

1. The National Childhood Vaccine Injury Act (NCVIA) requires health professionals to report

a. Adverse events after the administration of vaccines specified in the act, as described in the "Reportable Events Table" within the specified time period

b. Any event listed in the manufacturer's package insert as a contraindication to subsequent doses of the vaccine

2. In 1990, VAERS was set up to receive all reports of suspected adverse events caused by any U.S licensed vaccine

3. The VAERS depends on voluntary reporting by health professionals to

a. Identify rare adverse reactions not detected in pre-licensing studies

b. Monitor for Increases in already known reactions

c. Identify risk factors or pre-existing conditions that promote reactions

d. Identify particular vaccine lots with unusually high rates or unusual types of events

B. Medwatch, the FDA's Medical Products Reporting Program established in 1993, is a voluntary system for health care providers. However, manufacturers and distributors of FDA approved drugs, biologics, radiation-emitting devices, special nutritional products dietary supplements, infant formulas, and devices are mandated to report problems to the FDA. The goals of the program are to increase awareness of reporting of medical product induced diseases and the importance of reporting to clarify what should be reported, to make reporting as easy as possible, and to provide feedback to health professionals [10-15].

1. Importance of reporting

a. The incidence of ADRs, occurs at a high rate in health care today.

(1) Generally, it is reported that 3%-11% of all hospital admissions can be attributable to ADRs, although some studies report the figure to be as high as 29%.

(2) The likelihood that a patient will experience an ADR while hospitalized is reported in the literature to be in a range from 5%-25%.

b. Prevention of ADRs is an important strategy in health care. It has been estimated that atleast one third of all ADRs may be preventable. It has been further noted that preventable ADRs tend to be the most costly to treat and cause the greatest degree of patient morbidity

(1) Future ADRs can be prevented in individual patients by careful and consistent documentation in patient records

(2) A program that tracks ADRs can help discover previously unidentified trends. These trends can be used within the institution to develop programs of prospective intervention to prevent reoccurrence of the reaction in the patient populations that are at similar risk.

c. Recognition of previously undiscovered ADRs attributable to a drug is particularly true in the case of newly marketed products.

(1) Although clinical trials are generally effective in assessing efficacy and risk to benefit ratio, inherent limitations exist in premarketing trials.

(a) The trials are usually relatively short in duration and don't effectively mimic the exposure patients would experience if using the drug as a chronically administered agent.

(b) Drug-drug interactions and use in patients with concomitant disease states may not be tested for in these trials

(c) The small size of the trails (usually 1000-3500 individuals) is insufficient to detect rarely occurring adverse reactions.
(d) Racial and ethnic groups may not be participating in the same numbers as represented in the general population.
d. Prompt recall in cases of product problems are accomplished when the MedWatch Program is used to report product problems or device defects.
2. What should be reported?

ADRs that are serious, even if causality is not proven, including

1) A patients death that is suspected of being a direct outcome of an ADR
2) A life-threatening event
3) An initial or prolonged hospitalization
4) A significant, persistent, or permanent change or disability/incapacity
5) A congenital anomaly (including those occurring in a fetus)
6) Other problems that are not listed in the manufacturer's package insert as a known side effect

b) Malfunctioning medical devices such as heart valves, latex gloves, dialysis machine, ventilators and problems with nutritional products.
c) Product problems that can result in compromised safety or quality, including product contamination, mislabelling, unclear labelling, poor packaging, potency problems, and questionable stability
d) Counterfeit or suspected counterfeit drugs.
e) Adverse events, with food, herbs, vitamins, cosmetics or dietary supplements, although CAERS is the preferred reporting system
f) Adverse events owing to blood products, allergenics, gene therapy, human tissue and cellular products and xenotransplantation products
g) Medication errors
3. Confidentiality of both

Adverse reactions can be classified in seven different ways. The following classifications are available for different class as mentioned below:

Pharmacological classification

Type A (Augmented): This is the commonest type (up to 70%) of ADR which is predictable by the pharmacological mechanisms eg., hypotension by betablockers, hypoglycaemia caused by insulins or oral hypoglycaemics, or NSAIDs induced gastric ulcers. These type of adverse drug reactions are dose dependent hence forth severity increases with dose. Such ADRs are preventable in most part by slow introduction of low dosages. Sometimes referred to as Type 1 ADRs.

Type B (Bizzare): This type of ADR is not expected from the known pharmacological mechanisms e.g; hepatitis caused by halothane, aplastic anaemia caused by chloramphenicol neuroleptic malignant syndrome caused by some anaesthetics and antipsychotics. Such ADRs are unrelated to dose. Sometimes referred to as Type 2 ADRs.

Type C (Continuous Drug Use): This type of ADR occurs as a result of continuous drug use, such type of ADR may be irreversible, unexpected, unpredictable, eg. Tardive dyskinesias by antipsychotics, dementia by anti-cholinergic medications.

Type D (Delayed): This type of ADR is characterized by the delayed occurrence even after the cessation of treatment, eg. Corneal opacities after thioridazine, ophthalmopathy after chloroquine or pulmonary/peritoneal fibrosis by methyserzide.

Type E (End of Dose): This type of ADR is usually characterized by withdrawl reactions. Such ADRs occur typically with the depressant drugs, e.g., hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawl; first dose hypotension caused by alphablockers (Prazosin) or ACE inhibitors.

Type F (Failure of Therapy): This type of ADR results from the ineffective treatment, eg., accelerated hypertension because of inefficient control. This may also be called as lack of efficacy [20-22].

Type H (Hypersensitivity): Allergic or hypersenstitivity reactions are those adverse reactions that have an immunologic basis, Pseudoallergic reactions appear clinically as allergic reactions; however, an immunologic mechanism has not been demonstrated. DeSwarte suggested that the following eight criteria are helpful in distinguishing allergic reactions

1. Allergic reactions occur in a minority of the patients receiving the drug
2. Observed manifestations don't resemble the pharmacologic actions of the drug
3. Prior exposure may have been tolerated without adverse effect. Allergic reactions rarely occur after less than 1 week of therapy. However, after sensitization, the reaction develops rapidly after reexposure.
4. The reaction may be manifested by a spectrum of allergic phenomena: a variety of skin rashes, anaphylaxis, serum sickness- like reactions, pulmonary reactions, pulmonary reactions, hepatitis, drug fever, interstitial nephritis, and connective tissue disorders.
5. Small doses of the suspected agent or agents with similar structure activity relationships may reproduce the reaction.
6. Eosionophilia may be present.
7. Occasionally, specific antibodies may be detectable.
8. The reaction resolves spontaneously, if the medication is quickly discontinued.

Systematic identification of Adverse Reactions

Step 1: Review of published literature

a) Does the medication's package insert list the adverse reaction?
b) What other related adverse reactions are noted in the package insert?
c) Do Common pharmacology of therapeutics textbooks associated the adverse experience with the suspected medication?
d) Are there any published reports in the primary literature that associate the adverse experience with the suspected medication?
e) How long has the product been marketed? Most adverse reactions are reported during the first 2-3years after introduction. Products marketed for many years without an association of the suspected reaction casts doubts on a true association.

Step 2: Identification of other etiologies

a) What underlying patient factors (disease states, concurrent medications, nondrug interventions) may aggravate a pre-existing condition, which mimics an adverse reaction?

Step 3: Chronologic sequence of events

a) Determine the start time and date of all medications
b) Calculate the onset of the drug reaction in relation to the suspected medications
c) Does the occurrence of a pharmacologic reaction correspond to the attainment of peak or toxic serum concentrations

Step4: Drug levels

a) Can one readily determine the suspected drug's (or its metabolities) concentrations in biologic fluids?
b) Are serial concentration determinations warranted?
c) Is the incidence of the suspected adverse experience dose dependent?

Step 5: Dechallenge

\a) Does the severity or seriousness of the adverse reaction warrant discontinuation of the medication or a substantial decrease in dosage?

b) If so, does the intensity and the duration of the reaction change?

c) Could the development of drug tolerance cause a spontaneous decrease in the suspected adverse experience?

Step 6: Challenge

a) Are the consequences of re-administration minor enough in nature to warrant a rechallenge to elicit the reaction?
b) If so, what happened following the rechallenge?

Step 7: Previous patient medication history

a) Does the patient have a history of allergic disorders or medication allergies to related compounds?

Step8: Therapeutic decision making

a) Review the answers to the previous steps and weigh the therapeutic options available to you at this time. [9]

CAUSALITY ASSESSMENT OF SUSPECTED ADVERSE REACTIONS

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawl of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/likely: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawl (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawl may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which make a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/unclassified; A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment of the additional data are under examination.

Unassessable/Unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Despite every care taken in therapy, adverse reactions may occur that may be difficult to diagnose. As mentioned above the use of causality algorithms is advocated by some, and more recently computer-assisted methods using Bayesian logic and complex systems have been devised. None of these have found general support and most are too time-consuming for clinical practice. What the development and testing of algorithms has shown is that many diagnostic failures- both erroneously blaming a drug for a reaction and failing to recognise a drug as a cause of a reaction – occur because clinical data required for a diagnosis are missing. Most importantly this includes inadequate patient follow-up and lack of familiarity with the drug in question [23-28].

Seriousness/Severity of Adverse Reactions

In addition to the above definitions, there is also widespread agreement on the definition of seriousness and severity of a reaction. A serious reaction is any untoward medical occurrence that at any dose:

- Results in death

- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or is life-threatening

Cancers and congenital anomalies or birth defects should also be regarded as serious, as should medical events that would be regarded as serious if they had not responded to acute treatment [23-25]. The term 'severe' is often used to describe the intensity (severity) of a medical event, as in the grading 'mild', 'moderate' and 'severe'. Thus a severe skin reaction is not usually "serious".

ISSUES AND CHALLENGES FACED BY DEVELOPING COUNTRIES

1. As most drugs are developed in the west, most of the efficacy data are based on the Caucasians, with little or no information available on the Asians
2. There is no data on ADRs that may occur due to the interaction between the established medicines and traditional, herbal medicines and vaccines used locally
3. ADR reporting for traditional and herbal medicines, especially the multi-component and adulterated ones is not done seriously and reports present are negligible
4. Attrition from local manufacturers who usually manufacture generics in carrying the burden of Pharmacovigilance when innovator products are taken off the market for economic reasons. Inaddition, most of them don't care to invest in ADR monitoring, as they believe they deal with off-patent products. But ADRs associated with generics although less in frequency can still arise.
5. Moreover alot of sensitization and setting up of new systems will consume resources such as good labs, patient's ability to pay for tests, infrastructure for proper causality assessment, identification of funding agency and certainty of funding, etc [21-28].

SUCCESS FACTORS

The success of any Pharmacovigilance system depends upon the following factors:

1. Public awareness on need to report suspected ADRs.
2. Government support and well-defined policies with proper financial assistance presence of national coordinator and an advisory committee
3. Trained health care workers
4. Quality control of laboratories
5. Free and open communication between public and the policymakers
6. Ability to have free flow of information, i.e inquiries, feedback, etc.

DETECTION AND MONITORING OF ADR

In India, Drugs Controller's Office when giving permission for a new drug to be marketed in India does specify that any and all adverse reactions should be brought to its notice. How effective this specification has been in terms of obtaining reliable data on adverse reactions to drugs is not known. As a matter of fact, while one wonders at the paucity of adverse reactions reported in the Indian literature, occasionally one is also surprised at the unjustified or alleged reactions reported of drugs which would not stand elementary scientific scrutiny. Some teaching medical institutes in Delhi, Bombay, Vellore and perhaps other areas do have a system for reporting of adverse reactions. Usually such schemes are sponsored by the pharmacology departments. This may be a reflection of the supposedly nihilistic attitude of the academic clinical pharmacist or an acceptance by the clinicians that their difficult drug problems must be solved by clinical pharmacist. In these institutes probably all adverse reactions to drugs are to be reported on a special form. It would be highly optimistic to consider that even in these institutes significant percentage of adverse reactions are actually reported [28-32].

ADR MONITORING SYSTEMS

The International Conference on Harmonisation defines ADR as any noxious unintended , and undesired effects of a drug, that occur at doses used in human for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. ADR Monitoring Systems: Structural and Functional Aspects

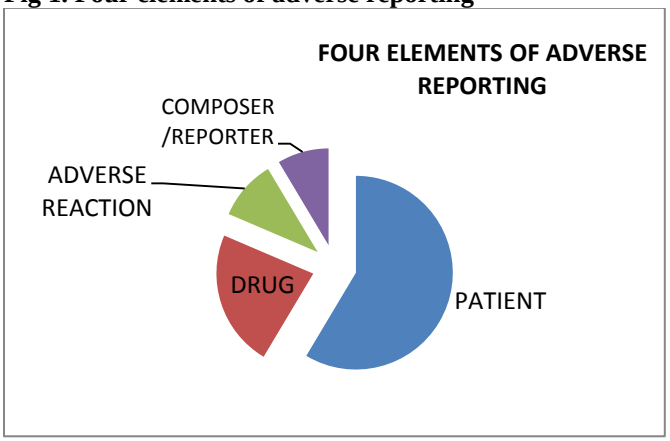
The pharmacovigilance concept liaisons on three pillars :

- ❖ Collecting new drug information from reliable scientific resources such as marketing authorization holders, healthcare professionals, consumers, international/public bodies, journals, published and updated literature, etc.
- ❖ Classifying and analyzing the above information
- ❖ Circulating its contents as well as any action taken on specific drug to all health sectors [33-35].

Four Elements of ADR Reporting

Any ADR report should have the following four main elements.

Fig 1. Four elements of adverse reporting



However, recent publications have shown that about half the ADRs, could be avoided with greater prescription care.

TERATOGENICITY

From the Greek root *'Tera'* meaning a foetal monster, the word Teratology is derived. The science which deals with the harmful effects of physical and chemical agents on the developing foetus is known as Teratology. Teratogenicity due to drugs and chemicals is a serious type of adverse drug reaction because it is manifested in the offspring at the time of delivery and is attributable to maternal medication during pregnancy. Interest in this field of study was intensely stimulated all over the world soon after the Thalidomide tragedy which took an epidemic form in Europe and Australia in 1961, when several thousand malformed babies were reported to be born to mothers who had received the drug during pregnancy. While evaluating experimentally the teratogenic potential of a drug, the clinical Pharmacologist is faced with a formidable research problem because the chances of applying data obtained from animals to man are meagre. Hence, the clinicians are striving to explore the potential teratogenicity of drugs through statistical evaluation of surveys carried out on families in which congenitally malformed children are born [36-37].

General Principles

The established general laws of teratogenesis are:

1. The initial event in the production of teratogenicity is the cessation of development of the embryo in the region of injury.
2. Even in the absence of a hereditary basis for certain anomalies, any type of malformation could be produced in an embryo.
3. Teratogens act on undifferentiated primordium between the period of determination and that of differentiation.
4. The sensitivity of different tissues comprising the area of damage varies according to the nature of the teratogenic material.

In experimental teratology chickens, rabbits, rats, mice and hamsters are used frequently and dogs and monkeys occasionally. Though there is no definite opinion regarding the choice of the animal species to be employed in teratogenic experiments, yet it is desirable to have animals having similarities with man in respect to placentation, reproduction pattern, metabolism and enzyme systems.

For the teratological screening of a drug at least two animal species have to be employed, because the experimental data from one species cannot be extrapolated to another. The results of experimental teratogenesis may be complicated due to variability in the animal species or strain, inconstancy of the foetal response and the incidence of spontaneous malformations. Therefore the number of animals to be used must be as large as practicable and should be analysable statistically. As large doses of drugs may induce abortion or resorption of the foetus, it is imperative to explore teratogenicity in animals in a dosage similar to that used in clinical practice. For purposes of establishing the relationship between dose of a drug and its teratogenic effect, it is necessary to employ more than one dose. Since the teratogenic action of a drug may vary according to the route of administration, it is essential to use the route that is employed in therapeutics. As teratogenic agents manifest their actions during the period of organogenesis, the drug must be administered throughout the entire critical embryonic period. Since many physical agents and environmental factors adversely affect the developing embryo, it is essential to exclude hypo and hyperthermia, vitamin imbalance, malnutrition, viral infections and seasonal variations while experimentally assessing the teratogenicity of chemicals and drugs. The experimental techniques employed production of teratogenesis could be either *in vivo* or *in vitro.*

For obtaining meaningful data the teratologist must experiment carefully in standardised conditions during mating, verification of gestation and investigation of malformations. Though there is no unanimity regarding the choice of a standard of reference as yet, a teratogen such as an antitumor agent that is effective in animals as well as in man may be preferred.

Nature and Mechanism

The embryopathies produced by a teratogen are polymorphic in nature and all the three parts of the gastrula may be affected. The malformations produced by drugs and chemicals may involve several systems and organs e.g. Central Nervous System with the formation of anencephaly, hydrocephalus and spina bifida, face with cleft palate, eye with anophthalmia, microphthalmia and cataract, absence of ear or dysplasia, skeleton and limbs with absence of tail, axial torsion, club foot, syndactyly, polydactyly, phocomelia, amelia and viscera with umbilical hernia, atresia of the anus, cardiovascular defects and urogenital anomalies such as hydronephrosis and horseshoe kidney. Identical malformations may be caused by most of the drugs if administered at the same stage of embryonic development but some drugs may produce specific malformations in a definite organ. The teratogenicity produced by various drugs cannot be correlated with a particular chemical structure or pharmacological action. Drugs may produce teratogenicity either by direct action on the embryo or through a metabolite. A teratogen or its active metabolite may behave as an antimetabolite and interfere with biochemical processes by competitive inhibition of essential cellular components, and thereby produce birth defects. The mechanism of thalidomide teratogenesis may be due to its metabolites acting as competitive antagonists of glutamic or folic acid. Teratogenic drugs may produce their effects by influencing the metabolism of proteins and nucleic.

acids e.g. trypan blue raises serum c1 and p-globulins and lowers the albumin fraction, and the alkylating antitumor agents denature nucleoproteins and precipitate DNA. Teratogens may interfere with cell division e.g. colchicin, an antimitotic antitumor agent, interrupts cell division in metaphase. Foetal malformations may be correlated with chromosomal anomalies e.g. aminonicotinamide produces polyploidy and fragmentation of the chromosomes associated with cleft palate in the mouse. Different teratogenic agents if given at the same time may interact and produce potentiation or addition of their effects e.g.insulin and nicotinamide, and cyclophosphamide and 5-fluorouracil. Drug induced embryopathies in man may be influenced by a combination of genetic, metabolic and environmental factors [38-40].

Teratogenic Drugs

These could be classified into three groups :

I. Drugs which are teratogenic in man and laboratory animals:

(I) Hypnotics: Thalidomide. The organs derived from the mesenchyme arc chiefly affected by thalidomide. In man malformations are more common in the upper extremities which may be stunted to the state of stumps ending in deformed hands with the number of digits reduced to four. The lower limbs may also manifest reduction in the "umber of toes. All the joints are randomly aligned and the skeleton resembles that of a seal, hence this condition is called phocomelia. In addition, syndactyly and triphalangia may also be observed.

(2) Anticonvulsants: Diphenylhydantoin. It has been reported to cause hair lipand cleft palate in babies born to epileptic mothers who received this drug during pregnancy. Diphenylhydantoin produces ectrodactyly, cleft lip, cleft palate, hydronephrosis and hydrocephalus in mice.

(3) Antidepressants: Imipramine. Recently imipramine has been reported to be responsible for producing limb defects in a few cases. This drug has also been claimed to be teratogenic in the rabbit.

(4) Hormones:

(i) Androgens: In several published clinical reports, masculinisation of the female foetus has been attributed to administration of androgens during pregnancy. Inaddition to masculinisation of the foetus, testosterone may produce permanent oestrus in the rat at the time of adulthood.

(ii) Estrogens: Diethylstilbestrol masculinises the foetus when injected into the pregnant woman. In the mouse and rat oestradiol feminises the male and masculinises the female.

(iii) Progesterogens: Progesterone when given for maintaining pregnancy in women suffering from threatened abortions, has been held responsible for masculinising effects upon the female foetuses. Masculinisation of the foetus in the rabbit has also been reported following administration of 17-ethinyltestosterone, a synthetic progesterone.

(iv) Cortisone: It has been reported to give rise to birth defects in man such as cleft palate, gastroschisis, hydrocephalus and Fallot's tetralogy. In the mouse and rabbits cortisone produces palate and cardiac anomalies.

(v) Thyroid: Clinically excess of thyroid causes disturbances of fertility or gestation. In the rat thyroxine produces cataracts in the offspring.

(5) Hypoglycemic agents:

(i) Insulin: It seems that in human beings insulin is the least teratogenic of the known hypoglycemic agents.

(ii) Sulphonylureas: Tolbutamide and Chlorpropamide have been reported to be teratogenic in man. Tolhutamide produces absence of thumbs, syndactyly, malformed pinnae with meatal atresia, tetralogy of fallot and multiple internal deformities. In the mouse spina hifida and anophthalmia are observed when tolbutamide is given.

(6) Chemotherapeutic agents: Sulfonamides. Sulfioxazole has been reported to be teratogenic in man. Sulfadimethoxypyrimidine when administered to pregnant rats and mice produces malformations of the teeth and skull in the offspring.

(7) Antibiotics: Tetracyclines. They have been reported to teratogenic in man. Among the experimental animals the chick is more sensitive to the teratogenic actions of tetracyclines.

(8) Antitumor agents:

(i) Cyclophosphamide: It produced hand and foot defects in the foetus born to a patient receiving this drug. In the chick embryo and rabbit foetus, cyclophosphamide gives rise to malformations of the limbs.

(ii) Busulfan: Busulfan when administered to a pregnant woman has been reported to produce hypoplasia of the ovaries and thyroid in the offspring. In the rat busulfan is teratogenic and inhibits the male germinal line of the adult leading to sterility in the progeny.

(iii) Aminopterine: I t p r o d u c e s anencephaly and club foot in man and cleft palate and anencephaly in the rat.

(iv) 6-Chloropurine: It produces a circular constriction of the body located at the origin of the forelimbs in man and rat.

II. Drugs suspected to be teratogenic in man though lacking experimental evidence.

(1) Anticonvulsants: Trimethadione. It has been suspected to be teratogenic in humans. Mothers receiving this drug for treatment of epilepsy during pregnancy have give" birth to offsprings with cleft palate, hydrocephalus and umbilical hernia. In laboratory animals no congenital anomalies could he produced with trimethadione.

(2) Antidepressants: Amitriptyline. Amitriptyline, an antidepressant related to imipramine has been also suspected to produce limb deformities in man.

(3) Anorectics: Phenmetrazine. Phenmetrazine, an appetite suppressant when used by pregnant women has been

reported to produce foetal malformation such as diaphragmatic hernia and limb deformities.
(4) Antihistamines: Meclizine. Meclizine when given to prevent vomiting in the early period of pregnancy has been suspected to produce foetal malformations. It has been show" experimentally that meclizine is not teratogenic in the rat.
III. Drugs proved to be teratogenic only in experimental animals:
(1) Mineral salts: In the chick, salts of barium and lead and sodium fluoride are teratogenic. Mercury salts produce anomalies in the mouse and chick.
(2) Alkaloids: Several alkaloids used in therapeutics have been shown to be teratogenic in experimental animals, e.g. caffeine [41-43] in the mouse, ergotamine and quinine in the rat and reserpine in the rabbit and the rat.
(3) Tranquillizers: Phenothiazines. Chlorpromazine and promazine produce teratogenic effects in the rat.
(4) Sedatives: Pentobarbital produces birth defects of the skeleton in the rat.
(5) Analgesics and Antiphlogistics :-Sodium salicylate and phenylbutazone both produce teratogenic effects in the rat.
(6) Antihistamines: Diphenhydramine and cyclizine are teratogenic in the mouse, rat and the rabbit.
(7) Antitumor agents:
(i) Nitrogen mustard: In the rat it causes deformed limbs, syndactyly and exencephaly and in the mouse atrophy of limbs, polydactyly, hydrocephalus and cleft palate.
(ii) Chlorambucil: It produces syndactyly and torsion of tail in the rat and cleft palate and umbilical hernia in the mouse.
(iii) Urethane: Urethane, an antimitotic agent causes club foot in the rat and cleft palate and syndactyly in the mouse.
(iv) Actinomycin D: It causes exencephaly, anophthalmia, microphthalmia, cleft palate and spina bifida in the rat and exencephaly and spina bifida in the rabbit.
(v) Azaserine: It causes cleft palate, hydrocephalus, syndactyly and fusion of ribs in the rat.
(vi) 6 - aminonicotinamide: It is teratogenic in the rat and mouse [43 -47].

IS GENDER DIFFERENCE A RISK FACTOR FOR ADR?

It has been estimated that ADRs occur approximately in 3–5% of subjects taking a drug [18-22] but the gender's importance as a risk factor remains a matter of debate. A recent study, which reviewed 10 years (1986–1996) of ADR in a Canadian institution, reported that more than 70% of the 2367 patients assessed were females. Several reports have revealed that women are more exposed to ADRs than men and this is in line with the evidence that 8 of 10 drugs, which have been dropped out from US market, were responsible for more ADR in women than in men. This was still true also when the analysis was performed in the absence of drugs that are more used by females [23]. Female sex is a risk factor to develop long QT syndrome [24,25], a ventricular arrhythmia induced by different classes of drugs, e.g., antipsychotic, antiarrhythmics, H1 antagonists, antimicrobial and antimalarial agents [26], probably because women have a longer QT interval then men. Actually there are approximately 50 different drugs that can cause QTprolongation and torsades, most likely by blocking potassium ions currents of the heart. In single cell experiments, two repolarization currents, IKr (rapid delayed rectifier) and IK1 (inward rectifier), were measured and showed a lower outward current density in cells from female rabbit hearts, which may contribute to these sexbased differences [27]. In a small clinical trial the IKr blocking drug ibutilide was administered to normal human subjects and premenopausal women varied in response over their menstrual cycle, with greatest QT prolongation during the menses and ovulation phases. The change in QT length during the luteal phase was similar to the change in men [28]. Anorexigen druginduced cardiac valvulopathy has been reported to be more frequent in women [29], whereas blood dyscrasias are more frequent in men [30]. Furthermore, women generally predominate among patients with drug-induced liver injury [31] and also they appear to be more susceptible to neuropsychiatric ADR, gastrointestinal (especially with NSAIDs) [32] and cutaneous allergic reactions [33]. Finally, genito-urinary, sex hormones, antineoplastic and respiratory agents give more ADRs in females than in men . In conclusion, the majority of the studies indicate that females are more prone to ADR. This enhanced risk could be related tothe class of therapeutic agents, to the type of ADR, to the age and physiological status of female, but also to the fact that women are generally treated with doses that essentially reflect the results obtained by trials carried out mainly in men.

ROLES OF PHARMACISTS IN THE MANAGEMENT OF ADRS

- Monitoring acute/chronic disease patients who are at greater risk of developing ADRs
- Monitoring patients who are prescribed with drugs highly likely to cause ADRs
- Assessing and documenting the patients previous allergic status of the patient
- Assessing the patient's drug therapy for its appropriateness and drug related problem in ward
- Assessing possible drug/food interactions in multiple therapies
- Assisting healthcare professionals in the detection and assessment of ADRs
- Encouraging/stimulating health care professionals in the detection and assessment of ADRs
- Documentation of suspected reported cutaneous reactions for future reference

- Follow-up of patients to assess the outcome of the reaction and its management
- Obtaining feedback about the reported reaction in the hospital
- Educating healthcare professionals about the importance of reporting an ADR in the hospital
- Educating patients about drug related problems
- Creating awareness about ADRs amongst healthcare professionals, patients and the public
- Preparation and utilization of promotional materials
- Communication with other health care professionals such as nurses, PG students and community/Clinical pharmacist
- Presentation of reports in meeting and conferences
- Conducing workshops/conference/seminars on ADRs for healthcare professionals
- Dissemination of signals generated through publication of reports in bulletins/Newsletter or journals

STARTING A PHARMACOVIGILANCE CENTER: ACTIONS FOR IMPLEMENTATION IN THE COMMUNITY

Getting started

PV is all about drug regulation and rests on sound collaborative ties, co-ordination, communications and public relations. The most suitable location for setting up a PV center is dictated by the political goverance and its healthcare priorities, including willingness to do, law enactment, its enforcement, funding, organisation, staffing , training, and development. For national coordination of PV, governmental support and sustained monitoring is a must. A center can be started in a hospital or at any department, preferably in pharmacology, pharm D, medicine, clinical pharmacy or clinical toxicology. Initially it may be started in one hospital locally and then extended to other hospitals to cover the entire region which could communicate closely with a zonal center. All zonal centers in turn can report to the national nodal center which would collate the data gathered from the entire country and channel it to the Uppsala Monitoring Center (UMC), Sweden, within specified time line, for global referencing and use. If a center is handling data of an entire country right from the beginning, fool proof channels of effective communication should be ensured with clinicians. The center should have atleast one clinical pharmacologist, clinical pharmacist or a physican to start working.

Planning the basics

A blueprint should drawn up to establish and get a PV system to work. Care needs to be taken to establish the following.

Communication process

Getting in conversation with health authorities and local regional, national bodies and groups engaged in clinical medicine, pharmacology, toxicology, epidemiology, briefing them about the importance of the project and its applicability in modern therapeutics

Data acquistiation

Designing a template for ADR reporting and making available ADR reporting forms at all times, to hospital departments and general practitioners, on which they can furnish relevant information to the data bank of the center.

Dissemination

Producing printed handouts as well as conducting meetings or workshops in hospitals and academia to acquaint health care professionals about the definitions, goals, scope and methodology of the PV system to create awareness about its relevance in present times.

Establishment

Hiring the right qualified and interested staff, getting suitable place for accommodating them as well as the center, making arrangements for telephones, computers, printers, word processors, database management, bibliography support services and internet.

Internal education

Ensuring proper education and frequent updating of the staff belonging to the PV centers by training them in data collection, filtration, mining, verification, interpretation and coding of ADRs, medicines coding, causality assessment, signal detection, risk management and action in case of serious/fatal adverse drug events (ADE). Data mining is a relatively nascent interdisciplinary area which involves finding correlations and patterns among many fields in large databases with the aim of categorizing the data and summarizing identified relationship.

Database

Creating a safety stored, classified database which is retrievable and guarded by required degrees of confidentiality.

Promotion

To inculcate and promote the habit of reporting ADRs to the higher center, medical journals, health bulletins and other professional healthcare publications.

Networking

To encourage health care professionals to contact institutions working on a global scale in PV e.g. Uppsala Monitoring Centre (UMC) WHO Deparment of essential Medicines and Medicines Policy, Geneva, and net groups like international Network for the Rational Use of Drugs

(INRUD), E-Drug and Network for Rational Use of Medicines (NetRUM).

The Manpower and the machinery

To begin with, a PV center could start with an part time expert who can be a physician or clinical pharmacist with some secretarial support. Gradually, as the data traffic increases, a full time professional should be appointed to maintain the center and secretarial support expanded. The increase in the quantum of work, staff resource requirements are calculated by flatly assuming the time of assessment of a single case as one hour. For the smooth functioning of a PV center, professional with expertise in pharmacology, clinical medicine, epidemiology, toxicology prove to be fruitful. Additionally, the center requires a permanent secretariat to handle phone calls, database, and documentation of literature and coordination of activities like interfacing with related departments to maintain secretarial continuity for successful functioning of the center.

An advisory committee serves to get funding and support for the center, monitoring and evaluation, keeping a tab in the quality of the procedures relating to data collection and mining, data interpretation and publication information. The advisory committee may be represented by the disciplines of clinical medicine, pharmacology, toxicology, epidemiology, phytotherapy, pathology, drug regulation and quality assurance.

There are a few basic technological requirements for a PV center- uninterrupted electric supply, intercom, multiconnection telephone, computer, printer, FAX, internet, photocopier, which should be made available and care should be taken that these remain working at all times. Adequate back up factilities should be present so that work is not paralyzed in case of sudden break downs.

Data acquisition

PV at present thrives heavily on a regional/country wide reporting of suspected ADRs through spontaneous reporting system form motivated reporters. It usually picks up signals of rare, serious, Unprecedented ADRs.

Reports of suspected ADRs are taken in case report forms (CRF) which in PV is defined as a notification relating to a patient with an ADE (or laboratory test abnormality) suspected to be induced by a medicine. The CRF should be distributed to health care professionals across the area covered by a particular PV center regularly, and a suitable system has to be developed to ensure that the filled forms are either collected or could be posted free, or sent by email/FAX to the center, so that there is an uninterrupted and free flow of data [48-50].

A CRF should contain minimum following information

- Patient Age, gender, medical history in brief, ethnic origin (in some countries)
- ADE monitoring: detailed description (nature, localization, severity, characteristics),reports of investigations and tests, date of appearance, course, outcome
- Suspected medicines: Name (brand, formulation, ingredient, concentration, manufacture), dose, route of administration date of initiation of therapy/date of withdrawl of therapy, indications for use, and rechallenge in case of non serious ADEs
- Other medicines: All other medicines used by the patient (including self medication) including their name, dose, route, date of initiation and with drawl.
- Risk factors: eg: impaired renal function, past exposure to suspected medicines, history of allergy, and social drug use.
- Reporter: Name and address of the reporter (confidential and to be used for data completion, verification and follow up.

Health care professionals e.g. practising physicians pharmacist, nurses, dentists, and midwives are reliable sources of information. Pharmacists and nurses can illuminate on concomitant medication and history of medicine usage. It is imperative for pharmaceutical companies to report any ADRs of their products to regulatory authorities. In the event of patients directly reporting ADRs, it is always better to communicate with their physicians for better understanding and verification of data.

The reporting can be done from peripheral to the regional PV centers, which sweep a particular region, which in turn pool into the zonal database, the analysis of which reflects a gross national overview.The entire national data should be reported to UMC.

Bringing a reporting culture

Reporting of ADR is a continuous process and important to cultivate and sustain the attention and interest of healthcare workers so that it gets incorporated as a routine procedure in healthcare. The following measures may be adopted to give a fillip to reporting:

- Easy and free availability of prepaid reporting forms and other modes of reporting
- Duly acknowledging the receipt of ADR reports telephonically or through personal communication
- Providing journal articles, ADR bulletins, newsletters to reporters
- Actively involving the PV center staff in scientific meetings, undergraduate and postgraduate education
- Collaborating with other PV committees
- Collaborating with professional associations
- Utilizing PV data for development of clinical pharmacy and clinical pharmacology

TASKS OF PHARMACOVIGILANCE

Information service

One of the primary responsibilities of a center is to make high quality credible and latest medicine information available to health care professionals. For this, the center should have access to update and comprehensive literature database. The national centers should preferably have an online access to UMC database and be on the mailing list of ADR bulletins of WHO.

Reaching out

Newsletters, medicine bulletins, column from reputed medical or pharmaceutical journals may be chosen as routes of effective propagation of latest developments in medicine research and therapy to the healthcare professionals.

Appraisal

The ADR case reports obtained are evaluated by the center staff, employing the collective know-how of clinical medicine pharmacology, toxicology, and epidemiology.

Secondary prevention of ADRs

Secondary prevention of ADRs can be attempted by distribution of "patient alert cards" which are pocket size cards and could be carried round by patients. They provide relevant information about the medicines including ADRs and go along way in preventing ADRs.

Data Processing

Data is best managed electronically by computing, wherein data is entered in a hierarchical format according to product name, medicine name or therapeutic category. This facilitates recording detailed case information and easy retrieval. Internationally accepted terminologies regarding classification of medicines (Anatomical Therapeutic Chemical (ATC), International Nonproprietary Names (INN) and ADRs e.g. WHO Adverse Reaction Terminology (WHOART), Medical Dictionary for Regulatory Activity (MedDRA) should be used, so that the data can be globally shared.

Hypothesizing

This is one of the chief goals of PV center. Based on the case reports, the center should be able to generate hypothesis or detect a signal with regard to probable ADRs.

Medicine regulation

It is PV center's duty to keep a close eye on the new medicines launched in the market and follow them up to look for newer ADEs, issue warnings, unmask newer indications or changes or to advocate withdrawl of medicines in extreme cases. A center should actively take up such activities towards furthering the role of PV with periodic safety update reports (PSURs) registries, risk management minimization plans and improved communication with changes in label of medicines.

Funding

Money is required to fuel the PV center and it should have an officially approved guaranteed source, which is immune to political governance and economic fluctuations, to direct a steady flow of funds so that the progress of work is not hindered. The requiste financial support required for a particular PV center is estimated based on how big a population the center is schemed to cater and the anticipated rate at which it is going to generate reports. Additional monetary support may be sought from health insurance companies, academia, philanthropic organisations, and government departments with an interest in medicine safety.

It is good to start a program in high spirits, but what is more important is to continue with the tempo to sustain it. The sustainability of PV program in india can be well recognized by the fact that during one calendar year, not even a single ADR report was sent to UMC from a country of 1 billion, and India rates below 1% in PV as compared to the overall world average of 5%. It could be remedied by training our technical manpower in the latest developments in PV, identifying, and supporting centers of excellence across the country which can impart quality training in PV to the health care professionals. Efficient communication both in sharing our own findings with the global database and reaching feedbacks and analysed reports to the prescribers well in advance should be ensured.

NEED FOR PHARMACOVIGILANCE ACTIVITIES [34]

Pharmacovigilance studies of drugs that are on the market (Phase IV studies) produce crucial information. Phase I through III are conducted in a limited number of individuals (a few hundred) usually under favourable conditions i.e in the hospital, under close surveillance, over a short period, with few concomitant medications, and with few high-risk individuals (e.g children, older individuals, pregnant women, or patients with renal or hepatic failure).Marketed drugs are used in a far broader range of patients and circumstances, which may lead to the emergence of previously unrecognized ADRs. Rare ADRs (occurring for instance in 1/1000 individuals) are unlikely to be identified in pre-marketing studies. If the unrecognized ADR is serious, it may have devastating consequences. A drug that belongs to a widely used pharmacological class may be used in up to 100,000 individuals within the first month, so that a rare (1/1000) but serious ADR may occur in 100 patients. There is no clinical trial design or other evaluation method that is capable of eliminating the risk of serious ADRs occurring after marketing. Therefore, pharmacovigilance studies are essential to identify and to measure ADRs in order to prevent further occurrences. In some clinical trials are well suited to the validation of clinical effects but are of limited value for identifying ADRs.

Need For Pharmacovigilance

- Unreliability of preclinical safety data
- Well-controlled conditions
- Small and specific sample size

Changing pharmaceutical marketing strategies

- Aggressive marketing
- Direct to consumer advertising
- Launch in many countries at a time

Changing physician and patient preferences

- Increasing the use of newer drugs
- Increasing the use of drugs to improve the quality of life
- Shift of supervised to self-administered therapy

Easy accessibility

- Increasing conversion of prescription drugs to OTC drugs
- Easy access by internet
- Easy availability of complementary medicines
- Easy availability of substandard drugs

Limitations of Clinical Trail

Homogenous population sample

- Strict inclusion/exclusion criteria
- Subjects usually have single disease
- Specific groups of children, elderly and pregnant are excluded

Small sample size

- Detection of rare adverse event is difficult

Short duration of trial

- Limits the detection of long-term adverse effects

Inability to detect ADRs under real conditions

- Drug interaction
- Drug food interaction
- Large number of other unpredictable conditions
- Detection of risk factors [35]

REGULATIONS RELATING OF PHARMACOVIGILANCE IN INDIA

In India, a pharmaceutical company holding the marketing license should ensure that they have adequate pharmacovigilance system in place to ensure the responsibility and liability of their marketed products, as specified in schedule Y. When two or more marketed products are identical in all aspects except their trade names, each pharmaceutical company holding a marketing license is obliged to meet the pharmacovigilance obligations. This includes establishment and maintenance of appropriate pharmacovigilance system to collect, collate, and evaluate information about suspected adverse reactions. All these adverse reaction reports and the information about the benefit-risk analysis of a product need to be shared with DCGI.A pharmaceutical company can achieve this either by setting up in- house systems for pharmacovigilance or can enter into contractual arrangements with CROs Specializing in pharmacovigilance function for meeting their Pharmacovigilance obligations.

Schedule Y

The legislative requirements of Pharmacovigilance in India are guided by specifications of Schedule Y of the drugs and Cosmetics Act 1945. The Schedule Y also deals with regulations relating to pre-clinical and clinical studies for development of a new drug as well as clinical trial requirements for import, manufacture, and obtaining marketing approval for a new drug in india. Schedule Y was thoroughly reviewed and its latest amendment, dated 20th January 2005, Indicates the continued commitment of DCGI to ensure adequate compliance of pharmacovigilance obligations of the pharmaceutical companies for their marketed products as well as relating to the reporting of adverse events from clinical trials. The section entitled post marketing surveillance includes the requirement for submission of periodic safety update reports (PSURs), PSUR cycles, template for PSUR, and the timelines and conditions for expedited reporting [36].

REASONS FOR ADVERSE DRUG REACTION

Nowdays, Adverse Drug Reaction (ADR) problem is the outcome of a variety of factors: availability of a large number of drugs to the doctors, the inability of any physician to be expertly informed on all aspects of all new drugs, and the pressure by sales-promoters to create a demand for the drug, canvassing by detail men and even colleagues, and the persuasion of patients themselves to use the new drugs on them promptly before much becomes known about the human toxicity of the drug.

1) Age of "Drug explosion"
2) Lack of proper information about drugs
3) Sales pressures-advertising, sampling etc.
4) Canvassing by

i) 'Agents' or the 'detail-men'
ii) Doctors
iii) Colleagues
iv) Friends
v) Patients

5) Early wide spread use of drugs (37-40)

FIXED DRUG ERUPTION

Fixed Drug Eruptions (FDE), first described by Brocq, in 1894, It is characterized by recurrent round, erythematous or violaceous plaques measuring 2 to 10 cm in diameter and with well-defined borders that appear in the same location each time the culprit drug is taken and resolve after discontinuation of the drug. The lesions are distinctive; they appear within 24 h of the administration of the offending drug and consist of large, symmetrical, well-demarcated, and painful erythematous plaques. The lesions may be associated with macules or vesicules. These plaques reappear in exactly the same sites every

time the responsible drug is administered. The patient usually complains of a burning sensation, and the lesions fade without leaving any trace of pigment after 2-3 wk. The most common locations are the palms, soles, glans penis, lips, and groin areas. Another form of the reaction is called pigmenting fixed drug eruption. In this type of reaction hyperpigmented patches remain at the site of the lesions for months to years. The pathogenesis of fixed drug eruptions has not been fully elucidated. A serum factor may be implicated. Nonpigmenting fixed drug eruption is not related to porphyria or porphyria cutanea tarda. It can be caused by many different drugs (mainly sulfonamides, tetracyclines, naproxen, and salicylates) and chemically unrelated drugs can cause FDE in the same patient. The diagnostic hallmark is its recurrence at previously affected sites with repeated ingestion of the suspected drug [42,43].

When the acute phase subsides, there is usually residual hyperpigmentation that becomes more pronounced after each recrudescence [44]. FDE are common cutaneous drug reactions, frequently misdiagnosed, occurring in all ages, although more commonly in young adults 4. They are responsible for 10 % of all adverse drug reactions [46]. It is currently known that many drugs can cause FDE, but some seem to be more frequent. The most common implicated drugs are antibiotics, namely sulfonamides, and nonsteroidal anti-inflammatory drugs (NSAIDs) [41,47]. The pathogenic mechanisms of FDE are still not well defined, but CD8+ T cells seem to play a major role in initiating epidermal injury by producing interferon γ and interacting with other inflammatory cells. Even if a drug is responsible for activation of CD8+ T cells, it does not seem to be the antigen recognized by CD8+ T cells. The reason for recurrence of lesions at the same site may be explained by the persistence in situ of CD8+ memory T cells.

The involvement of CD8+ T cells may suggest a role for cell-mediated hypersensitivity in the pathogenesis of FDE. Co-trimoxazole (trimethoprim plus sulfamethoxazole) is one of the most commonly prescribed sulfonamide drugs. It is effective against gram-positive and gram-negative bacteria and various opportunistic pathogens. Unfortunately, adverse reactions such as erythematous rashes, urticaria, fever, neutropenia, thrombocytopenia, Lyell syndrome, Stevens-Johnson syndrome, and on rare occasions anaphylactic shock occur during its use and co-trimoxazole is a major cause of FDE.

Table 1. The vaccine chart [16-19]

Regulatory body responsible for ADR control	ADRAC	NDMC PVU	NPAC	JPC	MADRAC NDSMC	PVU	NADEMC MCC	SPC Moh
Related legislation	Yes	Yes	No	-	Yes	No	Yes	Yes
Guidelines available	Yes	Yes	Yes	-	Yes	Yes	Yes	Yes
Official forms	No	Yes	Yes	-	Yes	Yes	Yes	Yes
ADR Reporting responsibilities of the following	Yes							
MoH (mandatory)	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Others (mandatory)	No	No	No	No	No	No	No	No
Validation and follow-up of ADR reports by the MoH								
Investigation reporting time for spontaneous ADRs	≤15days	≤15days	≤15days	≤15days	≤15days	≤15days	≤15days	≤15days
PMS studies conducted	Yes	-	-	-	Yes	-	Yes	
Reporting between submission of application and grant of license	Yes	-	-	-	Yes	Yes	Yes	
Reporting between submission of application and grant of license	Yes	-	-	-	Yes	Yes	Yes	
Reporting of non-serious ADRs	No	-	Yes	-	Yes	No	No	No
Reporting to the WHO centers (mandatory)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

VACCINE ADVERSE EVENT REPORTING SYSTEM

24 Hour Toll Free Information 1-800-822-7967

P.O. Box 1100,Rocky

ille,MD 20849-1100

PATIENT IDENTITY KEPT CONFIDENTIAL

ForCDC/FDA Use Only

VAERS Number

Data Received

Patient Name

Last First M.I.

Address

City State Zip

Telephone No.(_)

Vaccine administered by (Name):

Responsible Physician

Facility Name/Address

City State Zip

Telephone No.(_)

Form completed by (Name):

Relation to Patient ☐ Vaccine provider ☐ Manufacture ☐ Patient parent ☐ Other

Address (if different from patient or provider)

City State Zip

Telephone No.(_)

1.State

2.Country Where administered

3.Date of birth

4.Patient age

Mm dd yy

5.Sex

☐ M ☐ F

6.Date from completed

mm dd yy

7.Describe adverse events (symptoms,signs,time course) and treatment, if any

8.Check all appropriate

- ☐ Patient died (date / /)
- ☐ Life threatening illness mm dd yy
- ☐ Required emergency room/doctor visit
- ☐ Required hospitalization
- ☐ Resulted in prolongation of hospitalization
- ☐ Resulted in permanent disability
- ☐ None of the above

9.Patient recovered ☐ Yes ☐ No ☐ Unknown

12.Relevant diagnostic tests/Laboratory data

10.Date of vaccination

mm dd yy

Time _____ PM

11.Adverse event onset

mm dd yy

Time _____ PM

13.Enter all vaccines given on date listed in No.10

	Vaccine(type)	Manufacturer	Lot number	Route/site	No.previous dose
a.					
b.					
c.					
d.					

14.Any other vaccinations within 4 weeks prior to the date listed in 10.

	Vaccine(type)	Manufacturer	Lot number	Route/site	No.previous dose	Dose given
a.						
b.						

15.Vaccinated at :

☐ Private doctor's office/hospital ☐ Public health clinic or hospital ☐ Military clinic/hospital ☐ Other/Unknown

16.vaccine purchased with:

☐ Private funds ☐ Public funds ☐ Military funds ☐ Other/Unknown

17.Other medications

18. Illness at time of vaccination (specify.)

19. Pre-existing physician-diagnosed allergies, birth defects, medial conditions (specify)

20.Have you reported this adverse event previously ?

☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children for 5 and under

22.Birth weight

_____ lb. _____ oz.

23. No. of brothers and sisters

21. adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother Or sister				

Only for report submitted by manufacturer / immunization project

24. Mfr. /imm.proj.report no.

25. Date received by mfr./imm. proj.

26. 15 day report ?

☐ Yes ☐ No

27. Report type

☐ Initial ☐ Follow-up

Health care providers and manufacturers are requested by law (42 USC 300 aa- 25) to report reactions to vaccines listed in the table of the reportable events following immunization

Reports for reactions to other vaccines or voluntary except when required as a condition of immunization grant awards.

VAERS FORM FOR REPORTING POSSIBLE ADVERSE DRUG REACTIONS

Table 2. Naranjo's Causality Assessment Scale

		Yes	No	Don'tKnow
1	Are there previous conclusive reports on this reaction?	+1	0	0
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4	Did the adverse drug reaction reappear when the drug readministered?	+2	-1	0
5	Are there alternative causes (other than the drug) that could solely have caused the reaction	-1	+2	0
6	Did the reaction reappear when a placebo was given?	-1	+1	0
7	Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	+1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10	Was the adverse event confirmed by objective evidence?	+1	0	0

Table 3. Examples of adverse drug reactions due to the influence of associated disease of inter current illness

CONDITION	DRUG (S)	POSSIBLE EFFECT OR RISK	MECHANISM
RENAL FAILURE	Aminoglycosides antibiotics	Ototoxicity	PKe
	Colistin	Neuropsychiatric reactions in chronic renal failure (better tolerated in acute renal failure)	PKe
	Tetracyclines	Rise in blood urea, aggraviation of renal insufficiency	PDI
	Digoxin	Digitalis toxicity	PKe
	Furosemide (fruseamide)	Risk of otoxicity (more likely with large doses)	
	Ethacrynic acid		
	Aspirin (acetyl salicyclic acid)	Enchances bleeding tendency of uraemica and may itself cause blood loss due to gastric mucosal irritation	PDd
NEPHROTIC SYNDROME	Clofibrate	Myopathy	PKd
	Prednisolone	Increased incidence of adverse effects	PKd
	Diuretics	Incautious use can precipitate acute renal failure	PDd
LIVER DISEASE			
Hepatic precoma	May precipitate encephalopathy		PDd
Cirrhotic oedema and ascites	Incautious use can precipitate encephalopathy		PDd
Obstructive jaundice	Enhanced response		PDt
Hepatitis cirrhosis	Severe CNS toxicity		PKm
Cirrhosis			
Hepatitis	Ergot poisoning		PKm
GASTRODUODENAL DISEASES			
Peptic ulcer	Risk of bleeding or perforation of a peptic ulcer		PDd
Acute gastroenteritis	Pregnancy may result		PKa
CARDIOVASCULAR			

DISEASES		
Heart failure	Aggravate or precipitate heart failure	PDd
	CNS toxicity if dose not reduced in advanced heart failure	PKm
Pulmonary heart disease	Digitalis toxicity	PDt
Myocardial ischaemia	Disturbance of cardiac rate, rhythm and conduction	PDd
Bradycardia Conduction abnormality	Cardiac standstill	PDd
Hypertension	Rise in blood pressure	PDd
	Fall in blood pressure	PDd
	Antagonise guanethidine-type antihypertensive agents with rise in blood pressure	
HAEMATOLOGICAL DISEASES		
Bleeding disorders	Increased risk of haemorrhage	PDd
Thromboembolic disorders	Many drugs can modify response of oral anticoagulants	PD
Inherited abnormalities of erythrocytes	Haemolytic anaemia in those with G6PD Deficiency	PDd
MEGALOBLASTIC ANAEMIA	Haemopoietic depression	PDd
PSYCHOLOGICAL DISORDERS Schizophrenia	May aggravate schizopheria	PDd
NEUROLOGICAL DISORDERS Myasthenia gravis	Aggravate muscle weakness	PDd
Epilepsy	May aggravate seizures	PDd
Cerbrovascular diseases	Ishaemic episodes	PDd
RHEUMATIC DISEASE	Increased incidence of drug reactions in general	PDd
Systemic lupus erythematosus (SLS)	Attack of gout	PDd
Hyperuricaemia	Acute bronchospasm	PDd
RESPIRATORY DISEASES Asthma		
Pulmonary heart disease	Digitalis toxicity	PDt
ENDOCRINE DISORDERS	May aggravate diabetes or make control more difficult	PDd
Diabetes mellitus		
Hypothyroidism	Enchanced response Decreased response	PK/PD PDt
Hyperthyroidism	Decreased response	
	Enchanced response	
Hypopituitarism	Precipated coma	PDt
OCULAR DISEASE		

Glaucoma (narrow angle)	Risk of precipitating angle closure glaucoma	PDd
Glaucoma (open angle)	Sudden rise in intraocular pressure	
Infections	Exacerbate infections	

Table 4. Adverse effects associated with different classes of antiretroviral drugs [33]

Class	Drug	Adverse Effects
NRTIs	Zidovudine	Anemia, Nausea, Rash, Myopathy, Dyslipidemia
	Stavudine didanosine	Nausea, lipoatrophy, DSPN, dyslipidemia, pancreatitis, lactic acidosis, hepatic steatosis, heart disease, DSPN
	Abacavir	HSR, hepatotoxicity, heart disease
	Tenofovir	Renal insufficiency, bone loss
NNRTIs	Efavirenz	CNS adverse effects, rash, hepatotoxicity, lipoatrophy, Teratogenicity, hypertriglyceridemia
	Nevirapine	Rah, HSR, Hepatotoxicity
	Etravirine	Rash, Hepatotoxicity
PIs	All PIs	Nausea, diarrhea, rash, Dyslipidemia, Insulin resistance, Hepatotoxicity
	Atazanavir	Jaundice, Scleral icterus, Nephrolithiasis
	Lopinavir fosamprenavir	Heart disease
Entry Inhibitors	Enfuvirtide	Injection site reactions, Pneumonia, HSR
	Maraviroc	Cough, fever, respiratory tract infections, rash, hypotension (Postural) Hepatotoxicity, HSR
Integrase Inhibitors	Raltegravir	Headache, Insomnia, Dizziness, Fatigue

Potential methods to screen drugs for their potential to cause idiosyncratic drug reactions

1. Screening for the formation of reactive metabolites

This is relatively easy to do and is likely to lead to safer drugs but has not been demonstrated.Furthermore, it is unlikely that all reactive metabolites are equal, until we understand the role of reactive metabolites in IDRs, it will be difficult to interpret the data

2. Using markers of cell stress to screen drug candidate

If the danger hypothesis is correct, there should be patterns of cell stress that predict the potential of a drug candidate to cause IDRs. Examples of potential markers include induction of glutathione transferases and quinine reductase. There is preliminary evidence to support this hypothesis but it is too early to be certain. The complexity of this system and particularly, of the immune system, cannot be duplicated invitro and thus invivo screening would be necessary.

3. Screening for specific markers of cell toxicity

Although standard markers of toxicity have not been accurate in predicating IDR potential, new markers, such as mitochondrial function, might be more specific.Further research is required to test this idea.

4. Using gene chips to determine patterns of gene expression that are associated with IDR potential.

This strategy has the advantage that is does not require prior knowledge of mechanisms and can examine many different genes. The disadvantage is that gene chips are relatively insensitive to small changes, which could be a particular problem when studying complex tissues, where the changes of interest will only occur in a subset of the cells and could. Therefore, be obscured. Different drugs will probably cause different patterns, and interpretation of many complex sets of data will be a lengthy process. However, such data might point to more specific biological markers that predict IDR potential [48].

BENEFITS OF PHARMACOVIGILANCE

Pharmacovigilance plays an important role in the rational use of medicines by providing information about ADRs in the general population. Knowledge of the adverse effects of drugs is important for effective treatment. Communicating the potential harm of drug use to patients is a matter of high priority and should be carried out by every prescriber. Information collected during the pre-marketing phase of drug development may not detect rare ADRs. The use of a drug during a clinical trial is under controlled conditions, Clinical trials generally enrolled a selected, limited number of patients [49-51].

CONCLUSION

Our review article suggesting that, drug related problem in the community as well as in hospital increased in developing and developed countries. Hence awareness should created among the public regarding proper usage of drugs and strengthen the pharmacovigilance program in every country.

REFERENCES

1. Hallas J, Harvald B, Worm J, Beck-Nielsen J et al. Drug related hospital admissions. Results from an intervention program. *Eur J Clin Pharmacol*, 45, 1993, 199–203.
2. Raschetti R, Morgutti M, Menniti-Ippolito F, et al. Suspect adverse drug events requiring emergency department visits or hospital admissions. *Eur J Clin Pharmacol*, 54, 1999, 959–63.
3. Mart`ın MT, Codina C, Tuset M, Carné X, et al. Problemas relacionados con la medicación como causa del ingreso hospitalario. Med Clin (Barc), 118, 2002, 205–10.
4. Hallas J, Harvald B, Gram LF, Grodum E, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Int Med*, 228, 1990, 83–90.
5. Trontell. Expecting the unexpected –Drug Safety, Pharmacovigilance, and the prepared Mind. *N Eng J Med*, 351, 2004, 1385-7.
6. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.London: European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit; 1995 [cited 2005 March 27]. Available from;http://www.emea.eu.int/pdfs/human/ich/037795en.pdf.
7. Singh H, Dulhani N, Kumar BN, Singh P et al. A pharmacovigilance study in medicine department of tertiary care hospital in Chhattisgarh (Jagdalpur). India. *J Young pharm*, 2, 2008, 95-100.
8. Barbara Symusiak-Mutnick Adverse drug reaction reporting Chapter 22, Page no: 490-497.
9. Randal LB. Adverse drug reaction chapter 65, Page no: 1030—1037.
10. Parthasarathi G, Karin NH, Milap CN. A Textbook of Clinical Pharmacy Practice,2nd edition 2005, Page no :84-102.
11. Sachdev Y. Status of adverse drug reaction monitoring and pharmacovigilance in selected countries. Indian J Pharmacol, 40, 2008, S4-S9.
12. Mehta DJ. Methods of Reporting Adverse Drug Reactions. *Ind. J. Pharmac*., 4 (2), 1972, 69-74.
13. Sisodia P. Teratogenic Effects of Drugs. *Ind. J. Pharmac*., 4, 1972, 51-56.
14. Baker JBE. The effects of drugs on the foetus. *Pharmacological Review*, 12, 1960, 37.
15. Chen RL. Experimental and Clinical Chemoteratomesis. *Advances in Pharmaco1ogy*, 4, 1966, 263.
16. Elegg DJ. Teratology. *Advances in Pharmacology*, 11, 1971, 409.
17. German. J, Kowal A. & Ehlers KH. Trimethadione, and Human Teratogenesis. *Teratology*, 3, 1970, 349.
18. Fattinger K, Roos M, Vergeres P, Holenstein C, Kind B, Masche U, et al. Epidemiology of drug exposure and adverse drug reactions in two Swiss department of internal medicine. *Br J Clin Pharmacol*, 49, 2000, 158–67.
19. Hurwitz N. Predisposing factors in adverse reactions to drugs. *Br Med J*, 1, 1969, 536–539.
20. Domecq C, Naranjo CA, Ruiz I, Busto U. Sex-related variations in the frequency and characteristics of adverse drug reactions. *Int J Clin Pharmacol Ther Toxicol*, 18, 1980, 362–366.
21. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*, 279, 1998, 1200–5.
22. Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. *Br J Clin Pharmacol*, 46, 1998, 505–11.
23. Women's Health. GAO report to Congressional Requesters 01-754, July 2001.
24. Owens Jr RC. QT prolongation with antimicrobial agents: understanding the significance. *Drugs*, 64, 2004, 1091–124.
25. Roden DM. Drug induced prolongation of the QT interval. *N Engl J Med*, 350, 2004, 1013–22.
26. Drici MD, Clement N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. *Drug Saf*, 24, 2001, 575–85.
27. Liu XK, Katchman A, Drici MD, Ebert SN, Ducic I, Morad M, et al. Gender difference in the cycle length-dependent QT and potassium currentsin rabbits. *J Pharmacol Exp Ther*., 285, 1998, 672–9.
28. Rodriquez I, Kilborn MJ, Liu XK, Pezzullo JC, Woosley RL. Drug induced QT prolongation in women during the menstrual cycle. *JAMA*, 285, 2001, 1322–6.
29. Naqvi TZ, Gross SB. Anorexigen-induced cardiac valvulopathy and female gender. *Curr Womens Health Rep*, 3, 2003, 116–25.
30. Montastruc JL, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. *Fundam Clin Pharmacol*, 16, 2002, 343–346.
31. Ostapowicz G, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*, 137, 2002, 947–54.
32. Neutel CI, Maxwell CJ, Appel WC. Differences between males and females in risk of NSAID-related severe gastrointestinal events. *Pharmacoepidemiol Drug Saf*, 8, 1999, 501–507.

33. Arminio Monforte D, Lepri A, Rezza AC, Pezzotti G et al . Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naïve Patients. *AIDS*, 14, 2000, 499–507.
34. Mrinmoy C, Vijay T. Starting a Pharmacovigilance center: Actions for implementation. *Journal of pharmacology and Pharmacotherapeutics*, 4, 2011, 295-299.
35. JeanLouis M, Agnes S, Isabelle L, Pascale et al. Pharmacovigilance for evaluating adverse drug reactions value, organization, and methods. *Joint Bone Spine*, 73, 2006, 629-632.
36. Deepa A. Pharmacovigilance obligations of the pharmaceutical companies in India. *Indian J Pharmacol*, 2008, s13-s16.
37. Meyler L. Side effects of drugs. IVth ed. *Excerpta Med. Found. Hague*, 5, 1963, 285-304 .
38. Modell W. Drug-induced diseases. *Ann. Rev. Pharmacol,* 5, 1965, 285-301.
39. Rosenthal ML. Sensitivity reactions to drugs. Thomas Springfield. Illinois. 1958, pp. l-5.
40. Wade OL. Adverse reactions to drugs. William Heinemann Medical Books Ltd., 1970, 1-10.
41. Mahboob A, Haroon TS. Drugs causing fixed drug eruptions: a study of 450 cases. *Int J Dermatol*, 37(11), 1998, 833-8.
42. Silva A, Proença E, Carvalho C, et al. Fixed drug eruption induced by paracetamol. *Pediatr Dermatol*, 18(2), 2001, 163-4.
43. Gruchalla R, Beltrani V. Drug-induced cutaneous reactions. Allergic skin disease – a multidisciplinary approach New York: Marcel Dekker Inc.; 2000, p. 319-21.
44. Vireder NS, Gangwani OP. Fixed drug eruption: Current concepts. *Int J Dermatol.*, 1987; 26(2), 1987, 67-74.
45. García-Doval I, Rosón E, Feal C, et al. Generalized bullous fixed drug eruption after influenza vaccination, simulating bullous pemphigoid. *Acta Derm Venereol*, 81, 2001, 450-451.
46. Puga J, Carazo E, Céspedes M, et al. Eritema fijo medicamentoso no pigmentado. *An Esp Pediatr*, 45, 1996, 642-4.
47. Ozkaya-Bayazit E, Bayazit H, Ozarmagan G. Drug related clinical pattern in fixed drug eruption. *Eur J Dermatol*, 10(4), 2000, 288-91.
48. Jack Uetrecht Screening for the potential of a drug candidate to cause idiosyncratic drug reactions. *Drug discovery today*, 18, 2003, 832-837.
49. Sachdev Yadav. Status of adverse drug reaction monitoring and pharmacovigilance in selected countries. *Indian J Pharmacol*, 40, 2008, s4-s9.