INTRODUCTION
A drug-induced disease is the unintended effect of a drug, which results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or require hospitalization. Drug-induced disease can result from unanticipated or anticipated drug effects. Disease also can occur from product impurities, as was the case with deaths attributed to the use of contaminated heparin in 2008. Vigilance on the part of regulatory authorities, drug manufacturers, clinicians, and patients is necessary to minimize the potential harm that is inherent in drug use.

The adverse events due to drugs are extensive and is not limited to drug induced diseases. Let us first of all look into various terminologies used to describe the untoward effects due to drugs.

1. Adverse Drug Reaction (ADR): The World Health Organization defines an adverse drug reaction (ADR) as any noxious, unintentional, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy.

2. Adverse event (AE): Medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related. The essential difference from ADR is that AE need not be causally related to the drug in use.

3. Unexpected adverse reaction (UAR): Usually adverse drug reactions of a drug will be described in the product information. UAR is not consistent with applicable product information or characteristics of drug.

4. Side effect: Unintended effect occurring at normal dose related to the pharmacological properties.

5. Serious adverse event (SAE): Any untoward medical occurrence that at any dose results in death, Life threatening situation, requires inpatient hospitalization or prolongation of existing hospitalization, results in deformity or incapacity. SAE is especially important when you are doing drug trials/drug development studies.

6. Serious Unexpected Suspected Adverse Reaction (SUSAR): It is an adverse drug reaction which is suspected but unexpected and serious.

Any drug may cause an adverse drug reaction. Undoubtedly, all drugs produce an ADR in someone who has used them.

HISTORY
Public and professional concern about drug induced diseases first arose in the late 19th century. In 1922, there was an enquiry into the jaundice associated with the use of SALVARSAN, an organic arsenical used in the treatment of Syphilis. In 1937 in the USA, 107 people died from taking an elixir of sulfanilamide that contained the solvent diethylene glycol. This led to the establishment of the Food and Drug Administration (FDA), which was given the task of enquiring into the safety of new drugs before allowing them to be marketed. The major modern catastrophe that changed professional and public opinion towards medicines was the thalidomide tragedy. The thalidomide incident led to a public outcry, to the institution all round the world of drug regulatory authorities, to the development of a much more sophisticated approach to the preclinical testing and clinical evaluation of drugs before marketing, and to a greatly increased awareness of adverse effect of drugs and methods of detecting them. With the adverse reactions some drugs have been withdrawn from use or for some the label has been changed.

ADVERSE DRUG REACTIONS
It is estimated that 3-5% of hospital admissions are caused by ADRs. The incidence of serious and fatal adverse reactions in hospital patients has been reported between 0.32% and 6.7%.

Adverse drug reactions is mainly divided into two groups, Type A and Type B.

Type A reactions: are expected exaggerations of the drugs known effect. These are usually dose dependent and predictable and account for the majority of ADRs. Characteristics Type A reactions include: higher than normal dose administered, impaired metabolism or excretion, or very sensitive individuals. These reactions are often found in the FDA approved product labelling.

Type B reactions: are idiosyncratic and usually unrelated to the drug’s known pharmacology. Normally they are not related to the dose, are unpredictable, uncommon, and usually more serious than Type A. Examples are carcinogen and teratogens. These reactions are more commonly reported after a drug has been on the market for a number of years.

OTHER DRUG REACTIONS
Dose related adverse reactions: Dose related adverse reactions have led to the concept of the therapeutic
index, or the toxic: therapeutic ratio. This indicate the margin between the therapeutic dose and the toxic dose. Examples of drugs with a low toxic: therapeutic ratio are anticoagulants (warfarin, heparin), hypoglycemic drugs (insulin, sulfonylurea), antiarrhythmic drugs (lidocaine, amiodarone), cardiac glycosides (digoxin, digitoxin), aminoglycoside antibiotics (gentamicin, netilmicin), oral contraceptives, cytotoxic and immunosuppressive drugs (cyclosporine, methotrexate, azathioprine), antihypertensive drugs (betaadrenoceptors antagonists, ACE inhibitors).

I. Pharmaceutical Variation: ADR occur because of alterations in the systemic availability of a formulation. Examples include phenytoin intoxication, by a change in one of the excipients in the phenytoin capsules from calcium sulfate to lactose, which increase the systemic availability of phenytoin.

ADR due to presence of a contaminant: Examples are pyrogens or even bacteria in intravenous formulations.

Out of date formulations: can sometimes cause adverse reactions, because of degradation products. Out-dated tetracycline causing Fanconi’s syndrome is an example.

II. Pharmacokinetic Variations

a. Pharmacogenetic Effects

1. Acetylation: Acetylation shows genetic variability. There are fast and slow acetylators.

Several drugs are acetylated by n-acetyl transferase. Fast acetylation is autosomal dominant and slow acetylation is autosomal recessive.

Drugs whose Acetylation is genetically determined are: Isoniazid, Hydralazine, Procainamide.

Dapsone, Some sulfonamides. Increased incidence of peripheral neuropathy is observed in slow acetylators of Isoniazid.

2. Oxidation: Oxidation also shows genetic variability. There are individuals with impaired oxidation and with normal oxidation. Impaired oxidation ones are called as poor metabolizers and the ones with normal are called extensive metabolizers.

3. hydroxylation: CYP2D6 is a cytochrome P450 enzyme and carries out Debrisoquine hydroxylation. Impaired hydroxylation of Debrisoquine is an autosomal recessive defect of this cytochrome. Drugs that are affected besides Debrisoquine are: Captopril, Metoprolol, Phenformin, Perhexitine, Nortryptiline

Poor hydroxilators are more likely to show dose related adverse effect of these drugs. In case of toxic metabolites risk would be greater in extensive hydroxilators.

Succinylcholine Hydrolysis: Succinylcholine is hydrolyzed by pseudocholinesterase. In some individuals pseudocholinesterase is abnormal and does not metabolize. In such cases drug persist in blood and continue to produce neuro muscular blockade for several hours. This result in respiratory paralysis called scoline apnoea.

b. Hepatic Disease

Adverse drug reaction due to impaired hepatic metabolism are not so common. Hepatocellular dysfunction, as in several hepatitis or advanced cirrhosis, can reduce the clearance of drugs like phenytoin, theophylline and warfarin. A reduction in hepatic blood flow, as in heart failure, can reduce the hepatic clearance of drugs that have an high extraction ratio for e.g. propranolol, morphine and pethidine. Reduced production of plasma proteins (for e.g. albumin) by the liver in cirrhosis can lead to reduced protein binding of drugs.

c. Renal Disease

If a drug or active metabolite is excreted by glomerular filtration or tubular secretion, it will accumulate in renal insufficiency and toxicity will occur.

d. Cardiac Disease

Cardiac failure, particularly congestive cardiac failure, can alter the pharmacokinetic properties of drugs by several mechanisms:

1. Impaired absorption, due to intestinal mucosal edema and a poor splanchnic circulation, can alter the efficacy of some oral diuretic, such as Furosemide.

Hepatic congestion and reduced liver blood flow may impair the metabolism of some drugs (e.g. Lidocaine).

2. Poor renal perfusion may result in reduced renal elimination (e.g. Procanamide).

3. Poor renal perfusion may result in reduced renal elimination (e.g. Procanamide).

4. Reduced in the apparent volumes of distribution of some cardio active drugs, by mechanisms that are not understood cause reduced loading dose requirements (e.g. Procanamide, Lidocaine, Quinidine).

III. Pharmacodynamic Variations

a. Hepatic Disease:

Hepatic disease can alter pharmacodynamic responses to drugs in several ways;

1. Reduced Blood Coagulation: In cirrhosis and acute hepatitis, production of clotting factor is impaired and patients bleed more readily. Drugs that impair blood clotting, that impair homeostasis, or that predispose to bleeding by causing gastric ulceration should be avoided or used with care for e.g. Anticoagulants and NSAIDS.
2. Hepatic Encephalopathy: In patients with, or on the border line of, hepatic encephalopathy, the brain is more sensitive to the effects of drugs with sedative actions. If such drugs are used, coma can result. It is therefore wise to avoid Opioids & other narcotic analgesics and barbiturates.

3. Sodium and Water Retention: In hepatic cirrhosis, sodium and water retention can be exacerbated by certain drugs. Drugs that should be avoided or used with care include NSAIDS, Corticosteroids, Carbamazepine and formulations containing large amount of sodium.

b. Altered Fluid And Electrolyte Balance

The pharmacodynamic effects of some drugs are altered by changes in fluid and electrolyte balance. Example; The toxic effect of cardiac glycosides are potentiated by both Hypokalaemia and Hypercalcaemia. The ClassI of Antiarrhythmic drugs such as Quinidine, Procainamide and Disopyramide are more arrhythmogenic if there is hypokalaemia.

NON-DOSE RELATED ADVERSE DRUG REACTIONS

Include
a. Immunological and
b. Pharmacogenetic mechanisms of adverse reactions.

IMMUNOLOGICAL REACTIONS (Drug Allergy)

Features of allergic drug reactions

There is no relationship to the usual pharmacological effects of the drug; There is often a delay between the first exposure to the drug and the occurrence of the subsequent adverse reaction; There is no formal dose-response curve; The illness is often recognizable as a form of immunological reaction like rash, serum sickness, urticaria etc.

There are genetic factors that make some patients more likely to develop allergic reactions than others: A history of allergic disorders HLA status (antigens on human lymphocytes).

Classified acc. to the classification of hypersensitivity reactions, i.e. into four types, types I-IV.

Type 1 Reactions (anaphylaxis; immediate hypersensitivity):

The drug or metabolite interacts with IgE molecules fixed to cells, particularly tissue mast cells and basophiles leukocytes. This triggers a process that lead to the release of pharmacological mediators like histamine, 5-HT, kinins, and arachidonic acid derivatives, which cause allergic response. Manifest as urticaria, rhinitis, bronchial asthma, angio-oedema and anaphylactic shock. Drugs likely to cause type 1 are Penicillins, Streptomycin, local anaesthetics etc.

TYPE II REACTIONS (CYTOTOXIC REACTIONS)

A circulating antibody of the IgG, IgM, or IgA class interact with an antigen formed by hapten. Complement is then activated and cell lysis occurs. Example: thrombocytopenia, haemolyticanaemia quinidine or quinine.

TYPE 111 REACTIONS (IMMUNE COMPLEX REACTIONS)

Antibody (IgG) combines with antigen i.e. the hapten-protein complex in circulation Complex thus formed is deposited in the tissues, complement is activated, and damage to capillary endothelium results. Serum sickness is the typical drug reaction of this type. Penicillins, Sulphonamides & Anti thyroid drugs may be responsible.

TYPE IV REACTIONS (CELL MEDIATED)

T-lymphocytes are sensitized by a hapten-protein antigenic complex. Inflammatory response ensues when lymphocytes come in contact with the antigen. E.g. Dermatitis caused by local anesthetic creams, topical antibiotics and antifungal creams.

PSEUDO ALLERGIC REACTIONS

Term applied to reactions that resemble allergic reactions clinically but for which no immunological basis can be found. Asthma and skin rashes caused by aspirin are the examples.

BLOOD DISORDERS

• Thrombocytopenia, neutropenia, hemolytic anaemia, and aplastic anaemia can all occur as adverse drug reactions.

RESPIRATORY DISORDERS

• Asthma occurring as a pseudo allergic reaction to Aspirin, other NSAIDS and Tartarzine is an e.g. adverse drug reaction.

PHARMACOGENETIC VARIATION CAUSING NON DOSE-RELATED REACTIONS

Red cell enzyme defects

Unusual drug reaction occur in individuals whose erythrocytes are deficient in any one of three different but functionally related enzymes such as glucose-6-phosphate dehydrogenase, glutathione reductase and methaemoglobin reductase.

LONG TERM ADVERSE EFFECTS

a. Adaptive Changes

Examples include development of tolerance to and physical dependence on the narcotic analgesics and the occurrence of tardive dyskinesia in some patients receiving long term neuroleptic drug therapy for schizophrenia.

b. Rebound and Withdrawal Phenomena

During long term therapy sudden withdrawal of the drug can result in rebound reactions. Examples are typical syndromes occurring after
sudden withdrawal of narcotic analgesic or of alcohol (delirium tremens), sudden withdrawal of Barbiturates result in restlessness, mental confusion and convulsions, Sudden withdrawal of β-adrenoceptors antagonists result in rebound tachycardia which can precipitate myocardial ischemia, Sudden withdrawal of corticosteroids results in syndrome of adrenal insufficiency.

**DELAYED ADVERSE EFFECTS**

**Carcinogenesis**

There are three major mechanisms of carcinogenesis:

1. **Hormonal:** incidence of vaginal adenocarcinoma is increased in daughters of women who have taken stilboestrol during pregnancy for the treatment of threatened abortions.

   Increased risk of breast cancers is about 50% and woman taking hormone replacement therapy (HRT) for more than five years.

2. **Gene Toxicity:** Occurs when certain molecules bind to nuclear DNA and produce changes in gene expressions. Examples: bladder cancer in patient taking long term cyclophosphamide, carcinomas of renal pelvis associated with phenacetin abuse, non lymphocytic leukemia in patients receiving alkylating agents such as melphalan, chlorambucil etc.

3. **Suppression of immune responses:** patients taking immunosuppressive drugs such as azathioprine with corticosteroids have increased risk of developing lymphomas.

**EFFECTS CONCERNED WITH REPRODUCTION**

**A. Impaired Fertility:** Cytotoxic drugs can cause female infertility through ovarian failure with amenorrhea.

    Reversible impairment can be caused by sulphasalazine, nitrofurantoin, MAO inhibitors and antimalarial drugs; Irreversible impairment, due to azosperma, can be caused by cytotoxic drugs, such as alkylating agents cyclophosphamide and chlorambucil. Male fertility can be reduced by impairment of spermatozoal production or function and can be either reversible or irreversible.

**B. Teratogenesis:** Teratogenesis occurs when a drug taken during early stages of pregnancy causes a developmental abnormality in a fetus.

   Drugs can affect fetus at 3 stages:

   1. **Fertilization and Implantation:** Conception to 17 days causes failure of pregnancy which often goes unnoticed.

   2. **Organogenesis:** 18 to 55 days of gestation- Most vulnerable period, deformities are produced

   3. **Growth and Development:** 55 days onwards—development and functional abnormalities can occur.

ACE inhibitors can cause hypoplasia of organs. NSAIDs may induce premature closure of ductus arteriosus

Different teratogenic drugs are:

Thalidomide, Methotrexate, Warfarin, Phenytoin, Phenobarbitone, Valproate Sod. Lithium, etc.

**Approach to adverse reactions:** Type A reactions include medication errors. Therefore, there may be some difficulty in deciding the correct reporting procedure. If the reaction is caused by a prescribing, administering or monitoring error, a medication error has occurred and medication error report should be completed.

If the patient develops an ADR when the prescribing, administering and monitoring are appropriately carried out, an adverse drug reaction report form should be completed.

The FDA compiles information on adverse drug events. If a medicine causes a serious adverse event due to a either medication error or ADR the FDA should be notified. If a medication is commonly associated with medication errors the FDA should be notified. This feedback is essential so that the package labeling can be updated and the risk benefit ratio of the drug may be better understood.

In order for drugs to obtain FDA approval they must be proven safe and effective. The 1962 amendment to the federal food, drug, and Cosmetic Act requires manufacturers to report adverse drug events detected in postmarketing settings to the FDA. The Food and Drug Modernization act of 1997 states that substantial evidence of drug effectiveness may consist of data from one adequate and well-controlled clinical investigation plus confirmatory evidence.

Most drugs are studied in less than 4,000 patients before FDA approval. Drug reactions that occur in less than 1 in 1000 patients are difficult to detect. Premarking trials generally excluded special populations such as children, elderly, and women of child bearing age. Most drug withdrawn from the market for serious side effects, are withdrawn within 1-2 years of FDA approval, as experience is gained in a larger population outside of the narrow confines of clinical trials.

**PHARMACOVIGILANCE PROGRAM INDIA**

In India, the national coordinating centre (NCC for pharmacovigilance is ALL Institute of Medical Sciences. Medical colleges and major centres are ADR monitoring centres which will report the ADRs to the NCC. If there is a significant ADR that will be reported to WHO pharmacovigilance collaborating centre in Upsala.