

ADVERSE DRUG REACTIONS

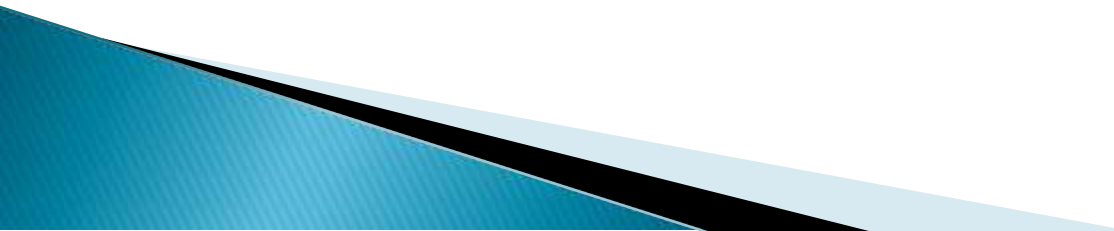


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ADVERSE DRUG REACTION (ADR)

Any noxious change which is

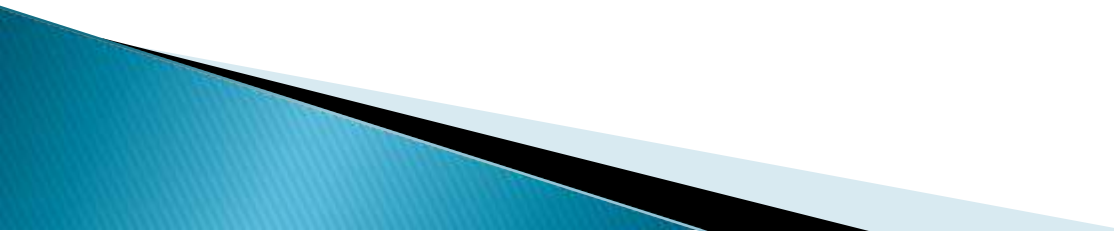
- ✓ Suspected to be due to a drug
 - ✓ At **doses normally** used in man
 - ✓ May requires treatment or decrease in dose or
 - ✓ Caution in the future use of the same drug
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ADVERSE DRUG EVENT (ADE)

Any untoward occurrence that may present during medical treatment,

But

Does not necessarily have a causal relationship with the treatment




► Incidence of ADR more in

- Polypharmacy
- Elderly
- Children
- Patient with multiple diseases
- Pregnancy
- Malnourished
- Immunosuppression
- Drug Abusers and addicts

► Develop

- Immediately
or
- Prolonged
medication
or
- After stopping

GRADING OF SEVERITY OF ADVERSE DRUG REACTIONS :

- **Minor** : No therapy, antidote or prolongation of hospitalization is required.
 - **Moderate**: Requires change in drug therapy, specific treatment or prolongs hospital stay.
 - **Severe**: **Potentially** life-threatening, causes permanent damage or requires intensive medical treatment.
 - **Lethal** : Directly or indirectly contributes to death of the patient.
- 

CLASSIFICATIONS OF ADR

1. **A (Augmented)**
2. **B (Bizarre)**
3. **C (Continuous)**
4. **D (Delayed)**
5. **E (Ending Use)**
6. **F (Failure of Efficacy)**

Broadly

Type- A (Predictable)- Based on pharmacological properties

Type- B (Non-predictable) – Based on Immunological response
and genetic makeup of person

TYPE A- AUGMENTED

- ▶ These are based on the pharmacological properties of the drug so can be predicted.
- ▶ They are common and account for 75% of ADRs
- ▶ Dose related and preventable mostly reversible.

Examples:-

- Anticoagulants (e.g., warfarin, heparin) – Bleeding
- Anti-hypertensives (e.g., α_1 -antagonists) – Hypotension
- Anti-diabetics (e.g. insulin) - Hypoglycemia

Predictable

TYPE B- BIZZARE OR UNPREDICTABLE

- ▶ Have **no direct relationship** to the dose of the drug or the pharmacological mechanism of drug action.
- ▶ Develop on the basis of:
 - Immunological reaction on a drug (**Allergy**)
 - Genetic predisposition (**Idiosyncratic reactions**)
- ▶ More serious clinical outcomes with higher mortality and morbidity.
- ▶ Mostly require immediate withdrawal of the drug.

Un-predictable

TYPE C – CHRONIC (CONTINUOUS) USE

- ▶ They are mostly associated with **cumulative-long term** exposure

Example:-

Analgesic (NSAID)– interstitial nephritis, papillary sclerosis, necrosis

Predictable

TYPE D – DELAYED

- ▶ They manifest themselves with significant delay
 - **Teratogenesis** -Thalidomide – Phocomelia
(flipper-like fore limbs)
 - **Mutagenesis/Cancerogenesis**

Others:

**Tardive dyskinesia – during L-DOPA
Parkinson disease treatment**



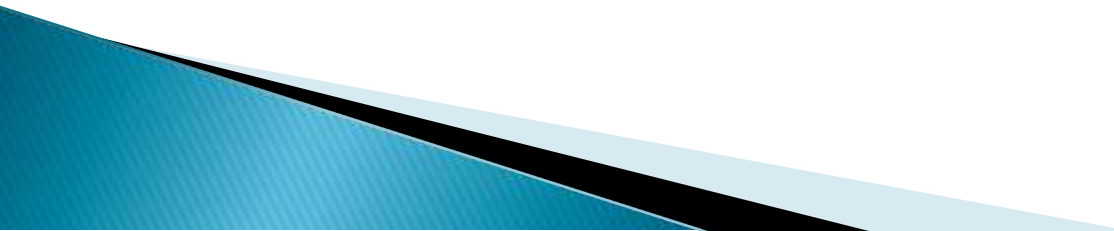
Predictable

TYPE E – END OF USE


- ▶ Drug withdrawal syndromes and rebound phenomena
 - Example – sudden withdrawal of long term therapy with β -blockers can induce rebound tachycardia and hypertension

Predictable

PHARMACOVIGILANCE (DAUP)

- ❖ The 'science and activities relating to the **d**etection, **a**ssessment, **u**nderstanding and **p**revention of adverse effects or any other drug related problems'
 - ❖ The information generated is useful in educating doctors and in the official regulation of drug use.
 - ❖ It has an important role in **rational use** of medicines, as it provides the basis for assessing **safety** of medicines.
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Various activities involved in pharmacovigilance are:


- ▶ **Postmarketing surveillance** and other methods of ADR monitoring such as voluntary reporting by doctors prescription event monitoring.
 - ▶ **Dissemination of ADR data** through 'drug alerts', 'medical letters,' advisories sent to doctors by pharmaceuticals and regulatory agencies.
 - ▶ **Changes in the labelling** of medicines indicating restrictions in use or statutory warnings, precautions, or even withdrawal of the drug.
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▶ The **Uppsala Monitoring Centre (Sweden)** is the international collaborating centre.

▶ In India,

- National centre is located at Ghaziabad
- Peripheral Centres at Medical college levels and tertiary and above hospitals
- Reports generated by doctors, paramedical staff--to peripheral centre...National centre...Uppsala Monitoring Centre...Compilation of data..analysis of data..causal association is confirmed..guidelines issued regarding the safe use of medicine or (restricted use or withdrawal from the market)

PREVENTION OF ADVERSE EFFECTS TO DRUGS (5A)

- ▶ **Avoid inappropriate use** of drugs .
 - ▶ **Appropriate drug administration (Rational Therapeutics)**
 - Dose
 - Dosage form
 - Duration
 - Route
 - Frequency
 - Technique
 - ▶ **Ask** for previous history of drug reactions and allergies
 - ▶ **Always** suspect ADR when new symptom arises after initiation of treatment. (No new drug for new symptom).
 - ▶ **Ask** for laboratory findings like serum creatinine etc.
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Categories of ADR :

- Side effects
- Secondary effects
- Toxic effects
- Intolerance
- Idiosyncrasy
- Drug allergy
- Photosensitivity
- Drug dependence
- Drug withdrawal reactions
- Teratogenicity
- Mutagenicity and Carcinogenicity
- Drug induced diseases (Iatrogenic disorders or Iatrogenicity)

Beware of – Iatrogenic, Idiosyncrasy, Idiopathic, Intolerance

SIDE EFFECTS


- ▶ Unwanted often unavoidable Pharmacodynamic effects.
- ▶ Occur at therapeutic doses.
- ▶ Predictable

Examples.

Benzodiazepines- Motor in coordination

H₁ Anti-histaminics- Sedation

An effect may be therapeutic in one context but side effect in another context

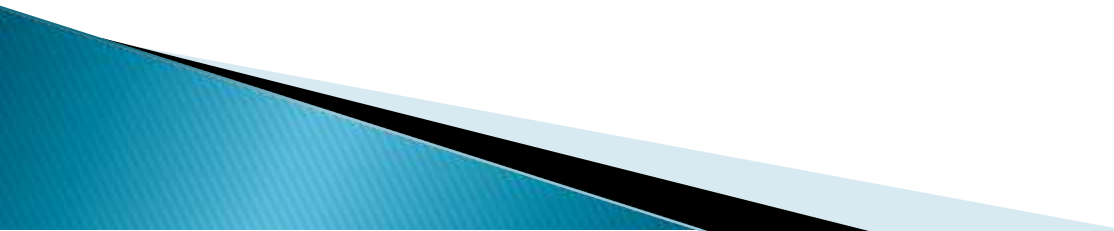
- Depression of A-V conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.
 - Constipation by codeine is side effect but can be used as therapeutic effect in patient with loose motions
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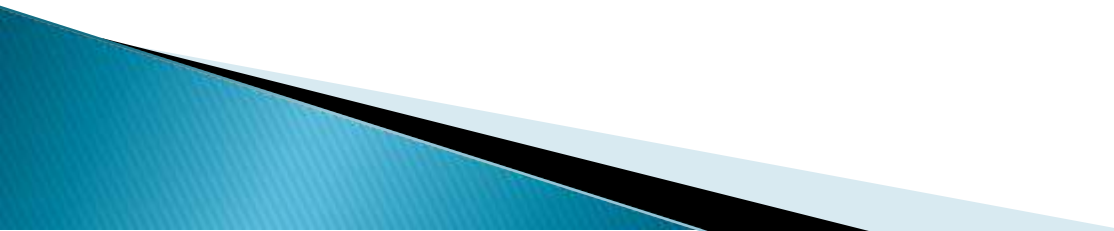
SECONDARY EFFECTS


- ▶ Indirect consequences of a primary action of the drug.
- ▶ E.g. corticosteroids weaken host defence mechanisms so that latent tuberculosis gets activated.

TOXIC EFFECTS (Poisonous effect)

It is the dose and duration which makes a substancepoison....

- ▶ Over dose or prolonged use.
 - ▶ The effects are predictable and dose related.
 - ▶ The CNS, CVS, kidney, liver, lung, skin and bone marrow are most commonly involved in drug toxicity.
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- ▶ Toxicity may result from extension of the therapeutic effect itself, e.g. complete A-V block by digoxin, bleeding due to heparin.
 - ▶ **Poisoning:** Poison is a substance which endangers life by severely affecting one or more vital functions.
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- ▶ Specific antidotes such as receptor antagonists, chelating agents or specific antibodies are available for few poisons.
 - ▶ For others as well as for those poisons which have a selective antagonist general **supportive and symptomatic treatment** should be done.
 - ▶ **These measures are:**
 1. **Resuscitation and maintenance of vital functions:**
maintenance of body temperature and blood glucose.
 2. **Termination of exposure (decontamination)**
 3. **Prevention of absorption** of ingested poisons.
 4. **Hastening elimination** of the poison by inducing diuresis or altering urinary pH
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INTOLERANCE

- ▶ It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses
- ▶ It indicates a low threshold of the individual to the action of a drug
- ▶ **Example:-** Only few doses of carbamazepine may cause ataxia in some people

Un-Predictable

IDIOSYNCRASY

- ▶ It is **genetically determined abnormal reactivity** to a chemical.
- ▶ The drug interacts with some unique **feature of the individual**, not found in majority of subjects, and produces the uncharacteristic reaction.

Example :-

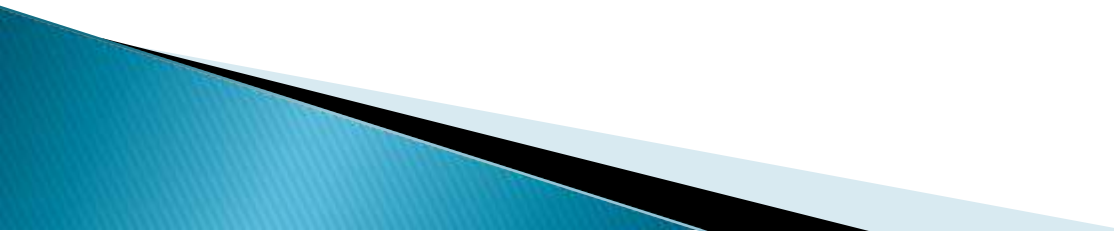
- ▶ Chloramphenicol produces non-dose-related serious aplastic anaemia in rare individuals.
- ▶ Barbiturates cause excitement and mental confusion in some individuals

Un-Predictable

DRUG ALLERGY

- ▶ It is also called **drug hypersensitivity**.
- ▶ It is an **immunologically mediated reaction** producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug.
- ▶ It generally occur even with **much smaller doses** and have a different time course of onset and duration.

Un-Predictable

- ▶ Allergic reactions occur only in a **small proportion of the population** exposed to the drug .
 - ▶ History of prior sensitization may or may not be evident.
 - ▶ The drug or its metabolite acts as antigen (AG) or more commonly **hapten** (incomplete antigen) and induce production of antibody (AB)/sensitized lymphocytes.
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TYPES OF ALLERGIC REACTIONS

A) HUMORAL

1. **Type I/ anaphylactic reactions.**
2. **Type-II / cytolytic reactions.**
3. **Type-III / retarded or Arthus reactions.**

B) CELL MEDIATED

Type-IV (delayed hypersensitivity) reactions.



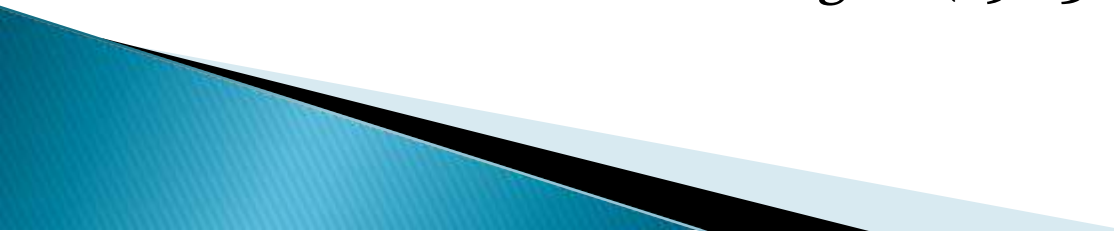
PHOTOSENSITIVITY

- It is a cutaneous reaction resulting from drug induced sensitization of the skin to **UV radiation**.
- The reactions are of two types: **Photo toxic** and **Photo allergic**

(A)Photo-toxic :-

- a) Drug or its metabolite **Accumulates** in the skin,
- b) absorbs light and undergoes a **Photochemical reaction** followed by
- c) **Photobiological reaction** resulting in
- d) Tissue damage (sunburn-like),
i.e. erythema, edema, blistering , hyper pigmentation, desquamation.

The shorter wave lengths (290-320 nm) are responsible



(b) Photo-allergic:

Drug or its metabolites induce a cell mediated immune response which on exposure to Light of

longer wave lengths (320-400 nm, UV -A)

Produces a papular or eczematous contact dermatitis.

Drugs involved are sulfonamides, sulfonylureas, griseofulvin, chloroquine, chlorpromazine



DRUG DEPENDENCE

- ▶ Use of drugs for personal satisfaction
- ▶ Higher priority than other basic needs, often in the face of known risks to health.

Physical dependence It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium.

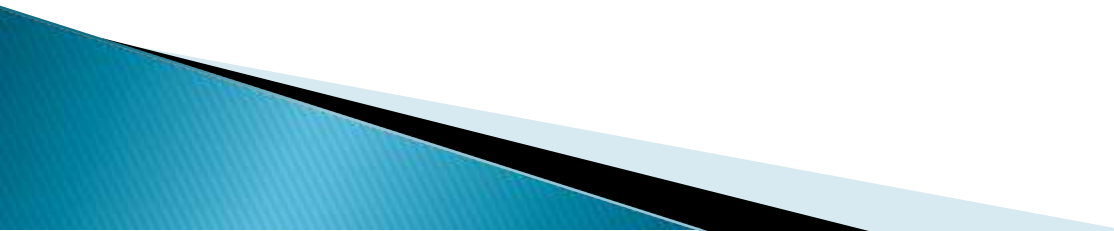
- ▶ Discontinuation of the drug results in a characteristic **withdrawal (abstinence) syndrome.**
- ▶ Drugs producing physical dependence are opioids, barbiturates and other depressants including alcohol and benzodiazepines

▶ Drug abuse :

Refers to use of a drug by self medication in a manner and amount that deviates from the approved medical and social patterns in a given culture at a given time.

▶ Drug addiction

It is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities



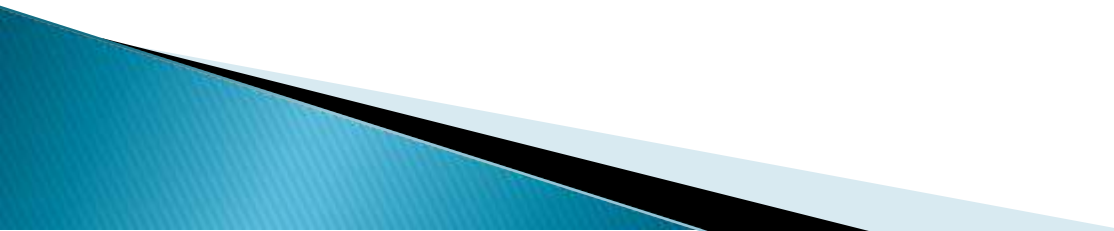
▶ **Drug habituation (Psychological dependence)**

It denotes less intensive involvement with the drug, so that its withdrawal produces only mild discomfort.

- ▶ Consumption of tea, coffee, tobacco, social drinking are regarded habituating, physical dependence is absent



DRUG WITHDRAWAL REACTIONS

- ▶ Sudden interruption of therapy with certain other drugs results in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used
 - ▶ **Example:** Acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy.
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TERATOGENICITY (Teratos- Monster)

- ▶ Drug to cause foetal abnormalities when administered to the pregnant mother.

- ▶ Drugs can affect the foetus at 3 stages-

(i) Fertilization and implantation-conception to

17 days- failure of pregnancy which often goes unnoticed.

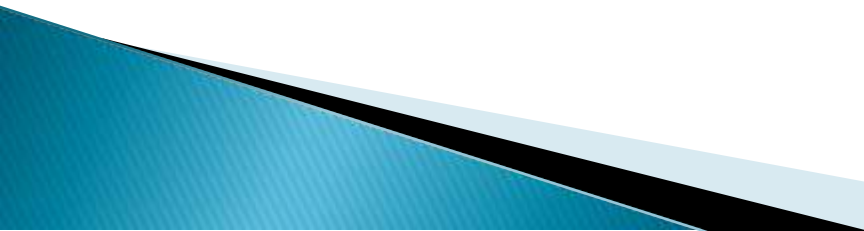
(ii) Organogenesis- 18 to 55 days of gestation most vulnerable period, deformities are produced.

(iii) Growth and development- 56 days onwards

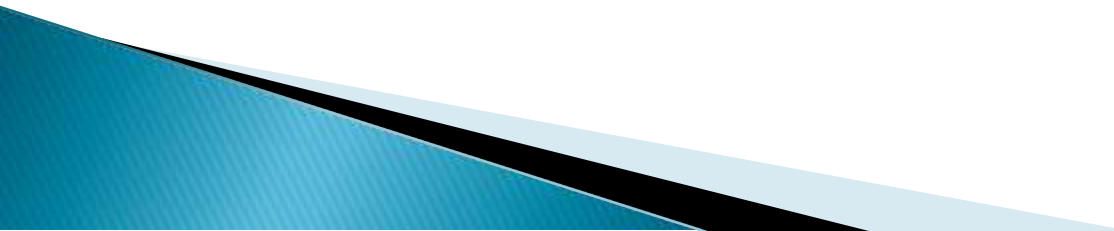
developmental and functional abnormalities can occur,

e.g. ACE inhibitors , Thalidomide, Warfarin, Barbiturates,.....

MUTAGENICITY AND CARCINOGENICITY

- ▶ Cause genetic defects and cancer respectively.
 - ▶ Reactive intermediates which affect genes and may cause structural changes in the chromosomes
 - ▶ Even without interacting directly with DNA, certain chemicals can promote malignant change in genetically damaged cells, resulting in carcinogenesis.
 - ▶ **Examples-** anticancer drugs, radioisotopes, estrogens, tobacco.....
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DRUG INDUCED DISEASES

- ▶ These are also called **Iatrogenic (physician induced)** diseases, and are functional disturbances (disease) caused by drugs .
 - ▶ **Hepatitis by isoniazid and Rifampicin**
 - ▶ **Peptic ulcer by salicylates and corticosteroids**
 - ▶ **Retinal damage by chloroquine**
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ADR REPORTING FORM

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO Central Drugs Standard Control Organization Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, FDA Bhavan, ITO, Kotla Road, New Delhi www.cdsc0.nic.in					(AMC/ NCC Use only) AMC Report No. _____ Worldwide Unique no. _____				
A. Patient Information 1. Patient Initials _____ 2. Age at time of Event or date of birth _____ 3. Sex <input type="checkbox"/> M <input type="checkbox"/> F 4. Weight _____ Kgs					12. Relevant tests / laboratory data with dates _____				
B. Suspected Adverse Reaction 5. Date of reaction stated (dd/mm/yyyy) _____ 6. Date of recovery (dd/mm/yyyy) _____ 7. Describe reaction or problem _____					13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc) _____				
14. Seriousness of the reaction <input type="checkbox"/> Death (dd/mm/yyyy) _____ <input type="checkbox"/> Life threatening <input type="checkbox"/> Hospitalization-initial or prolonged <input type="checkbox"/> Disability					<input type="checkbox"/> Congenital anomaly <input type="checkbox"/> Required intervention to prevent permanent impairment / damage <input type="checkbox"/> Other (specify) _____				
15. Outcomes <input type="checkbox"/> Fatal <input type="checkbox"/> Continuing					<input type="checkbox"/> Recovering <input type="checkbox"/> Recovered <input type="checkbox"/> Unknown <input type="checkbox"/> Other (specify) _____				
C. Suspected medication(s)									
5. No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known give duration) Date started _____ Date stopped _____	Reason for use of prescribed for
i.									
ii.									
iii.									
iv.									
5. No As per C	9. Reaction abated after drug stopped or dose reduced Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> NA <input type="checkbox"/> Reduced dose <input type="checkbox"/>					10. Reaction reappeared after reintroduction Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> NA <input type="checkbox"/> If reintroduced dose <input type="checkbox"/>			
i.									
ii.									
iii.									
iv.									
11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)					D. Reporter (see confidentiality section in first page) 16. Name and Professional Address : _____ Pin code : _____ E-mail : _____ Tel. No. (with STD code): _____ Occupation _____ Signature _____				
17. Causality Assessment					18. Date of this report (dd/mm/yyyy)				

Thank You

