Adverse drug reactions and safety reports

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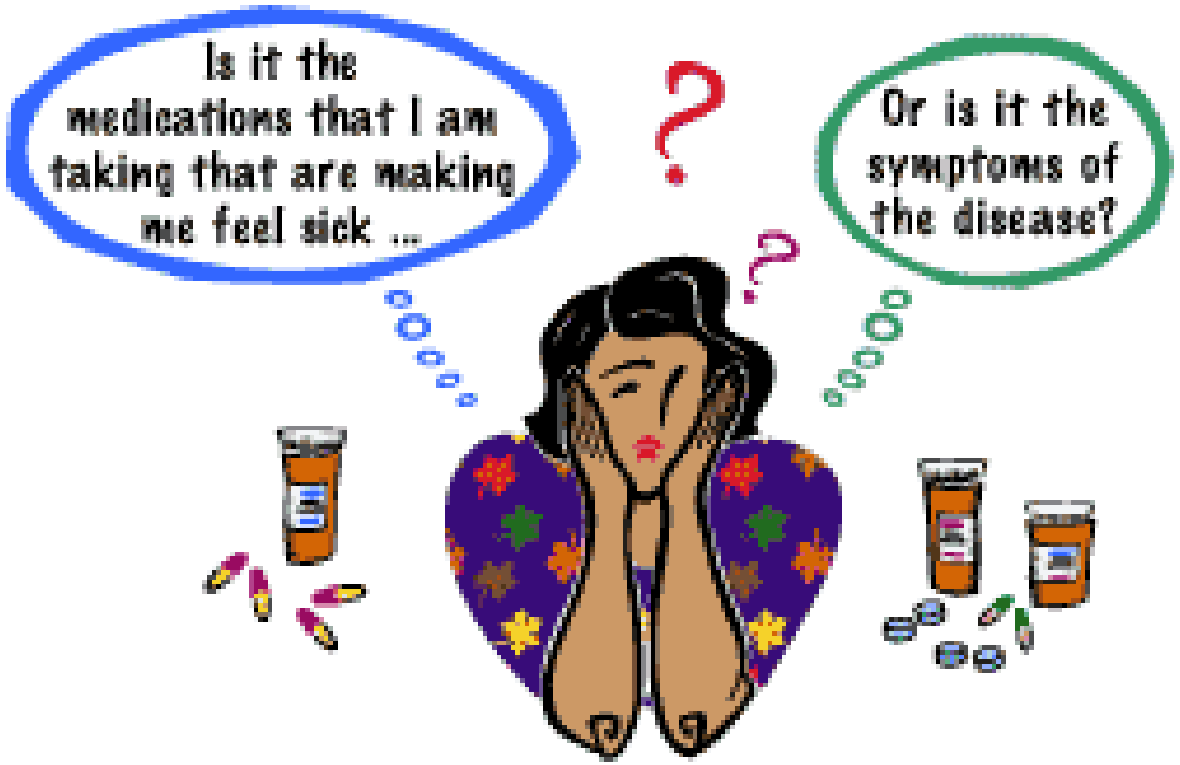
Professor

- Introduction
- Classification
- Examples
- Detection and reporting
- Causality assessment
- Management



“There is no drug with single effect”

ADR - WHO definition

"Any response to a drug which is **noxious and unintended**, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

A – Augmented

B – Bizarre

C – Continued use

D – Delayed

E – End of use

F – Failure of therapy

- **Predictable**
  Expected
  Type A

✓ Side effects

✓ Secondary effects

✓ Toxicity

- **Unpredictable**
  Unexpected
  Type B

✓ Hypersensitivity or allergy

✓ Genetically determined

✓ Ideosyncretic

Others – type C, D, E & F

- Predictable & dose dependant
- High incidence rate but low mortality
- Based on pharmacological properties of drug
- Preventable & reversible by reduction in dose
- Side effects, secondary effects & toxic effects

- Same action as therapeutic action – GTN - dilatation of blood vessels

  → relives the anginal pain (TU)

  → postural hypotension & throbbing headache (AE)

- Different than therapeutic action – promethazine

  → antiallergic action (TU) → sedation (AE)

- Same action TU – AE - codeine → constipation

  → Cough suppressant (AE))

  → Traveler's diarrhoea (TU)

Indirect consequences of primary action

- Tetracyclines –
  - → suppression of bacterial flora in GIT
  - → Superinfection
- CS –
  - → immunosuppression
  - → weakens host defense so risk of bacterial /fungal infections

Excessive PA due to overdose or prolonged use

- Gentamicin – nephrotoxicity
- Atropine – hallucinations, hyperpyrexia
- PCM – hepatic necrosis
- Sulfonamides – crystalluria
- Digoxin – complete AV block

- Unpredictable & non-dose dependant
- Uncommon & high mortality
- Mechanism unrelated to pharmacological effect
- Reduction in dose does not reduce it
    - Drug allergy
    - Genetically determined
    - Idiosyncrasy

- Immunologically mediated stereotype symptoms
- One drug – different types of allergic reactions - in different persons - of different duration

Type I reactions (IgE-mediated)

Type II reactions (cytotoxic)

Type III reactions (immune complex)

Type IV (delayed, cell mediated)

- Atypical peudo-choline esterase – succinyl choline apnea
- Hydroxylase polymorphism – INH induced peripheral neuritis or hepatotoxicity

- Halothan induced malignant hyperpyrexia
- Chloramphenicol induced aplastic anaemia

- **Type C - Chronic**

  Analgesic nephropathy

  Dyskinesias with levodopa

- **Type D - Delayed**

  Carcinogenesis, teratogenesis

- **Type E - End of dose response**

  Rebound hypertension with propranolol

  Withdrawal seizures by phenytoin

- **Type F – Failure of therapy**

Frequency of adverse drug reactions (CIOMS)

Very common	**>= 1/10**
Common (frequent)	**> = 1/100 and < 1/10**
Uncommon (infrequent)	**>= 1/1000 and < 1/100**
Rare	**>= 1/10000 and < 1/1000**
Very rare	**< 1/10000**

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly / Birth Defect
- Need of Intervention to Prevent Permanent Impairment or Damage (Devices)
- Other Serious and important Medical Events

Severe ??? Serious

New onset migraine

- lasting two days
- causing subject to stay in bed and miss work, unable to care for children

Not life threatening

No hospitalization

No persistent disability

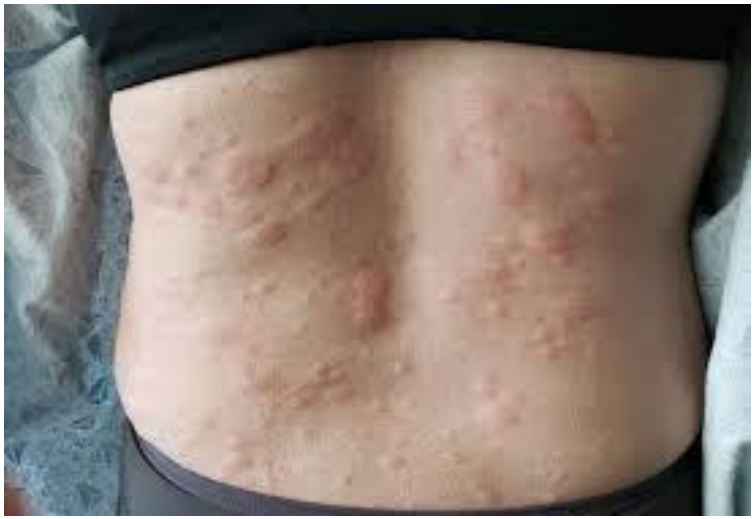
Not Serious

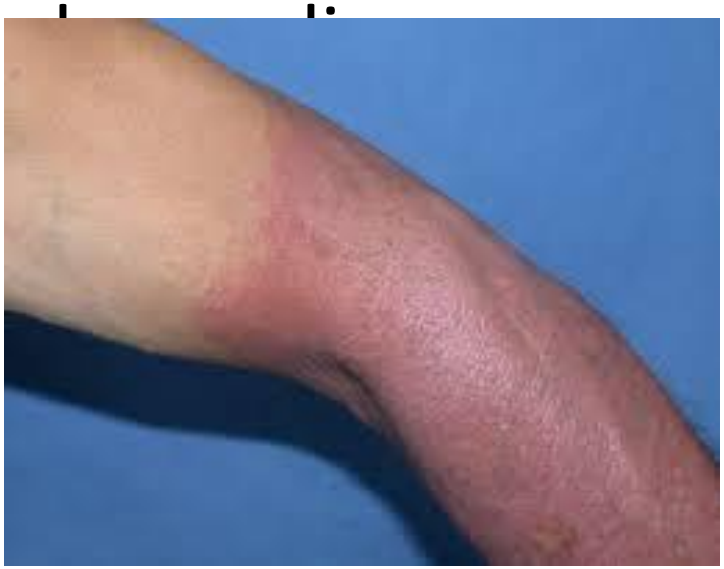
But, intensity is *Severe*

- Hereditary factors
- Associated diseases
- Simultaneous use of several drugs
- Very young or old age
- Pregnancy
- Breastfeeding

Examples - ADRs

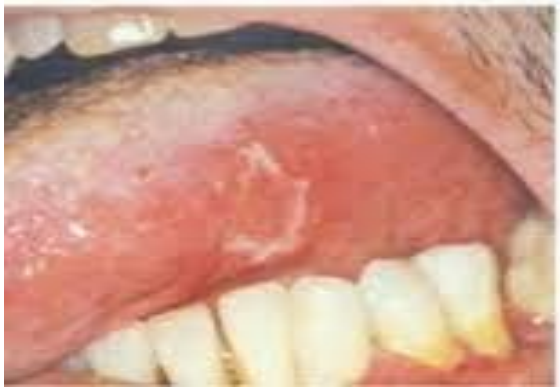
- Allergic reactions
  - Many drugs
- Photosensitivity
  - Demeclocycline,





- Anemia
- Leucopenia
- Aplastic anemia
- Thrombocytopenia
- Agranulocytosis

- Clozapin
- Carbimazole, propyl thiouracil
- ACE inhibitors



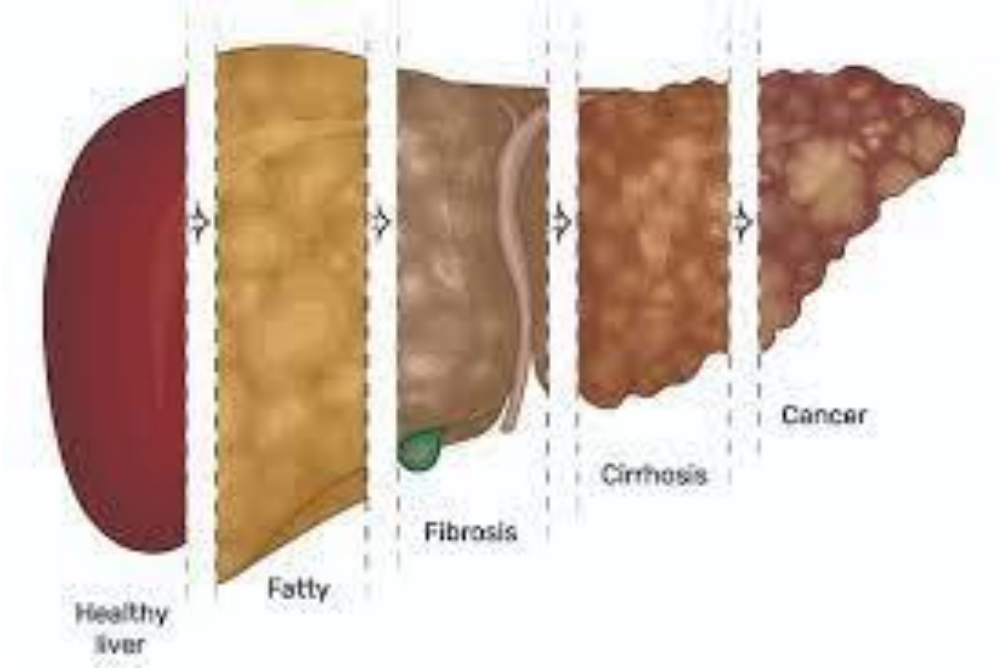
- Hemorrhage – Bleeding
- Thromboembolism

- Warfarin
- Heparin
- Streptokinase
- Estrogen

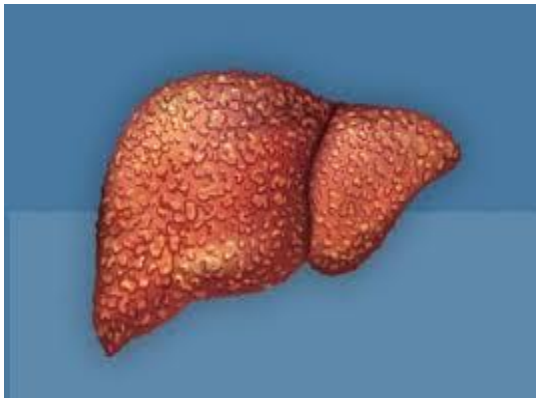
Direct effect

- **Predictable**
- Dose related
- Morphological changes
- Microvesicular fat deposit

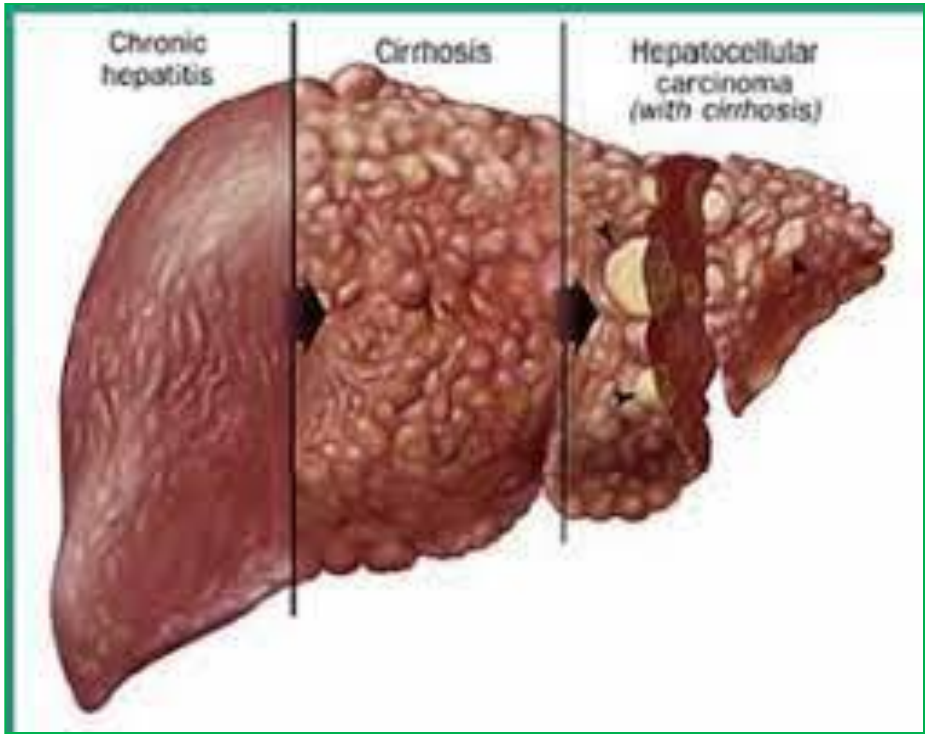
- Paracetamol
- Tetracycline



- **Non specific hepatitis** – Isoniazid, pyrazinamide, cotrimoxazole, phenytoin, Halothan – toxic metabolites
- **Sclerosing cholangitis** – floxuridine
- Anticancer drugs – cyclophosphamide, blusulfan **– hepatic sinusoidal occlusion**



- **Cholestatic jaundice** - OCP



- **Hepatic necrosis** – methyldopa
- **Cholestatic hepatitis** – chlorpromazine, amoxiclav, erythromycin
- Anti HIV drugs - **steatohepatitis**

Isoniazid

↓

Slow Acetylation - High blood level

↓

Acceleration of pyridoxine excretion

↓

More chances of peripheral neuropathy

↓

Add pyridoxine

(Liver dz, kidney failure, alcoholics, HIV, Diabetics)

↓

Rapid Acetylation - Low blood level

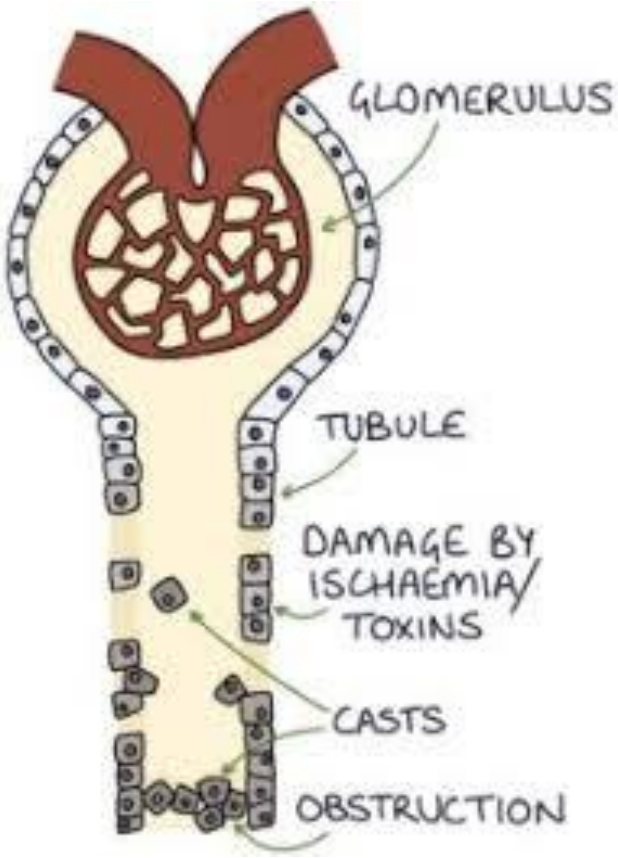
↓

Chemically reactive metabolite like acetyl hydrazine

↓

Severe hepatitis/ Acute Hepato cellular necrosis

- **Direct effect -** NSAIDs, Aminoglycosides, Heavy metals
- **Indirect effect –** diuretics – hypokalamia – renal tubular damage
- Cytotoxic drugs – hyper uricemia



- Sulfonamides, INH, rifampicin, phenytoin – acute or chronic renal failure

Cleft lip

Corticosteroids and phenytoin

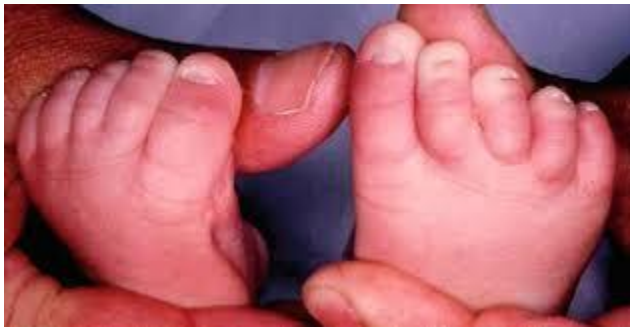
Teeth staining

Tetracycline

Fetal hydantoin syndrome

Cleft lip and palate

Phenytoin cuases digital hypoplasia and cleft lip and palate.



- Diethylstilbesterol – clear cell carcinoma of vagina in female offspring
- Estrogen – endometrial cancer

- Premature Battery Depletion in Certain Medtronic Pacemakers

PREVIOUS
reservoir retainer ring (clear)

UPDATED
reservoir retainer ring (black)

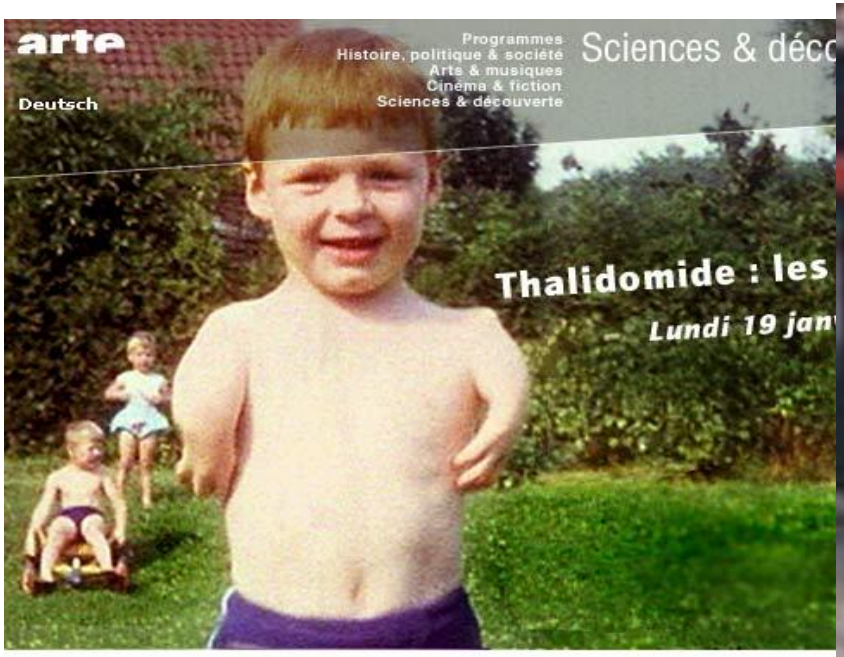
Image: Location of the retainer ring on the MiniMed™ 600 series insulin pump

- MiniMed™ remote controller (MMT-500 or MMT-503)
- August -2018
- Risk of Unauthorized individual to copy RF signals who in close proximity of an insulin pump user
- Potential health risks such as hypoglycemia if additional insulin is delivered beyond the user's insulin requirements

ADRs - Clinical implications :

- Recognition
- Prevention
- Management
- Reduce dose or withhold
- Effects of concomitant therapy
- Treat symptoms

- Duration, Date of onset, resolution
- Severity - Mild, Moderate, Severe
- Assessment - Serious / Non serious
- Relationship to study medication - Suspected / Not suspected
- Action taken – discontinued / dose
- Outcome - Recovered, Improving, Unchanged, Deteriorated, Permanent Disability, Death, Unknown



Thalidomide disaster

ADR Monitoring

Process by which data on ADR are collected, compiled and analyzed with the aim of optimizing drug therapy

- 30-50% are preventable
- Obvious interactions
- Use of contraindicated drugs
- Drug use in an inappropriate clinical indication or medically unnecessary

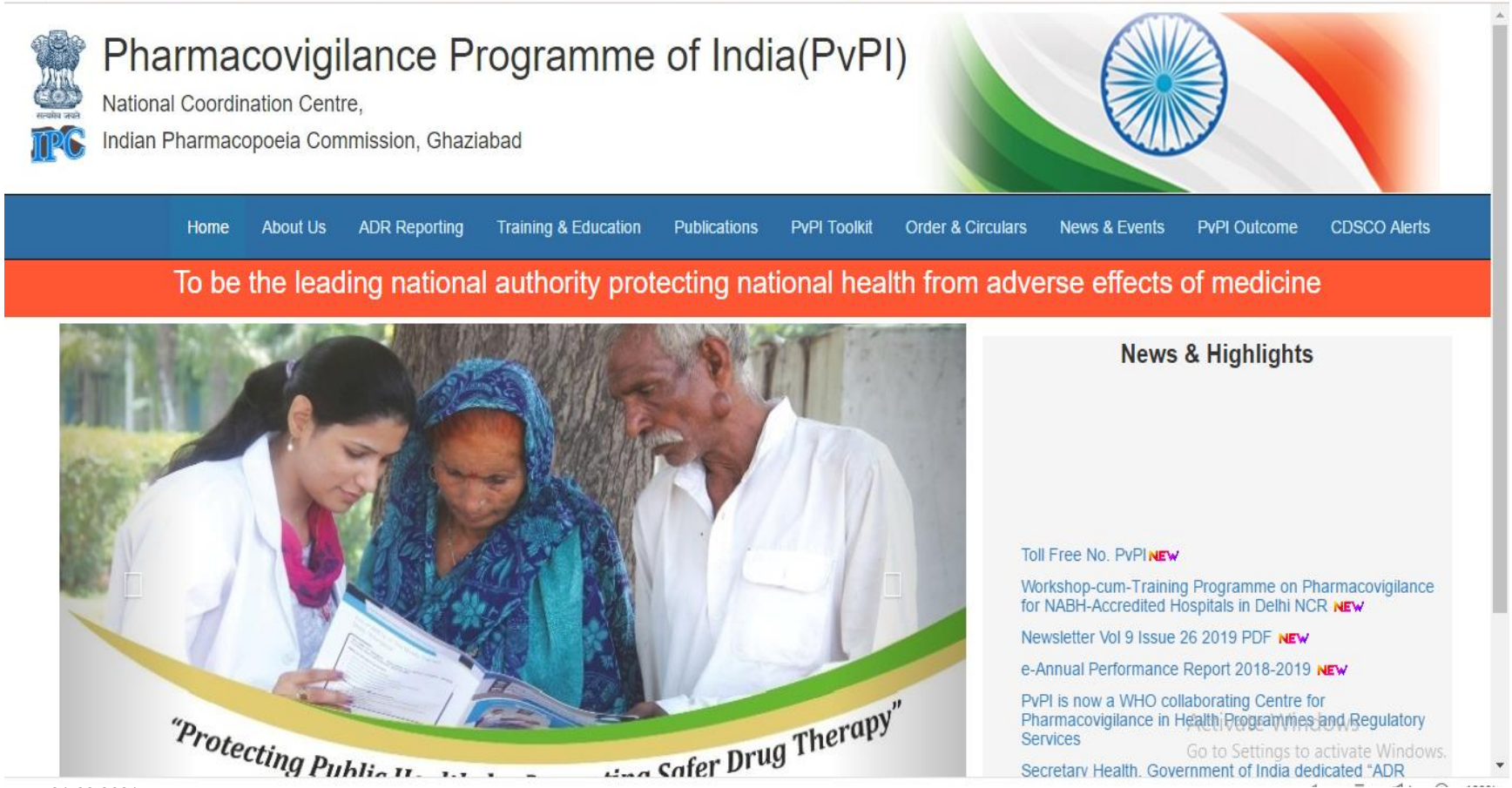
Indian Pharmacopoeia Commission (IPC) under the Ministry of Health and Family Welfare, Government of India

Objective

- Promote the quality of drugs and pharmaceuticals through standards setting in Indian pharmacopoeia (IP)
- Providing Indian pharmacopoeia reference substances (IPRS) to the stakeholders
- Rational use of medicines by bringing out national formulary of India (NFI)
- Ensure safety of medicines and medical devices through Pharmacovigilance programme of India (PVPI)

- **Sources of ADR reports**
- **Who should report?**
- **How to report?**
- **What ADR should be reported?**

https://ipc.gov.in/



SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

CDSCO
Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
Nirman Bhawan, New Delhi - 110011
www.cdsco.nic.in

For VOLUNTARY reporting of Adverse Drug Reactions by health care professionals

Report #

To be filled in by Pharmacovigillance centres receiving the form.

A. Patient information

1. Patient identifier initials _____ In confidence

2. Age at time of event: or _____ Date of Birth:

3. Sex: ☐ M ☐ F

4. Weight_____ Kgs

B. Suspected Adverse Reaction

5. Date of reaction started (dd/mm/yy):

6. Date of recovery (dd/mm/yy):

7. Describe reaction or problem

12. Relevant tests/ laboratory data, including dates

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

- ☐ Death (dd/mm/yy)_____
- ☐ Life threatening
- ☐ Hospitalization-initial or prolonged
- ☐ Disability
- ☐ Congenital anomaly
- ☐ Required intervention to prevent permanent impairment/ damage
- ☐ Other (specify)_____

15. Outcomes

- ☐ Fatal
- ☐ Recovering
- ☐ Unknown
- ☐ Continuing
- ☐ Recovered
- ☐ Other (specify)_____

C. Suspected medication(s)

Sl. No.	8. Name (brand and / or generic name)	Manufac-turer (If known)	Batch No. / Lot No. (If known)	Exp. Date (If known)	Dose used	Route used	Frequency	Therapy dates (if unknown, give duration)		Reason for Use or prescribed for
								Date started	Date stopped	
i										
ii										
iii										
iv										

Sl. No. As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced, dose
i										
ii										
iii										
iv										

11. Concomitant medical products and therapy dates including self medication and herbal remedies (exclude those used to treat reaction)

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address: _____

Pin code: _____ E-mail: _____

Cell No. / Tel. No. with STD Code: _____

Speciality: _____ Signature:

17. Occupation

18. Date of this report (dd/mm/yy)

Minimal information for regulatory reporting:

- an identifiable patient
- an investigational drug
- an identifiable reporter
- An adverse event

- Record all AEs in the CRF
- Report it to regulating authority
- Ensure adequate follow-up and
- Inform regulating authority

Causality assessment

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically(an objective and specific medical disorders or recognized pharmacological phenomenon)
- Rechallenge (if necessary)

Probable

- Event or lab abnormality, with reasonable time relationship during intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not necessary

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal lacking or unclear

Unassessable/ unclassifiable

- A report suggesting an adverse reaction
- Can’t be judged because of insufficient or contradictory information
- Report can’t supplemented or verified

Unlikely

- Event or laboratory abnormality with a time to drug makes a relationship improbable(but not impossible)
- Disease or other drugs provide plausible explanation

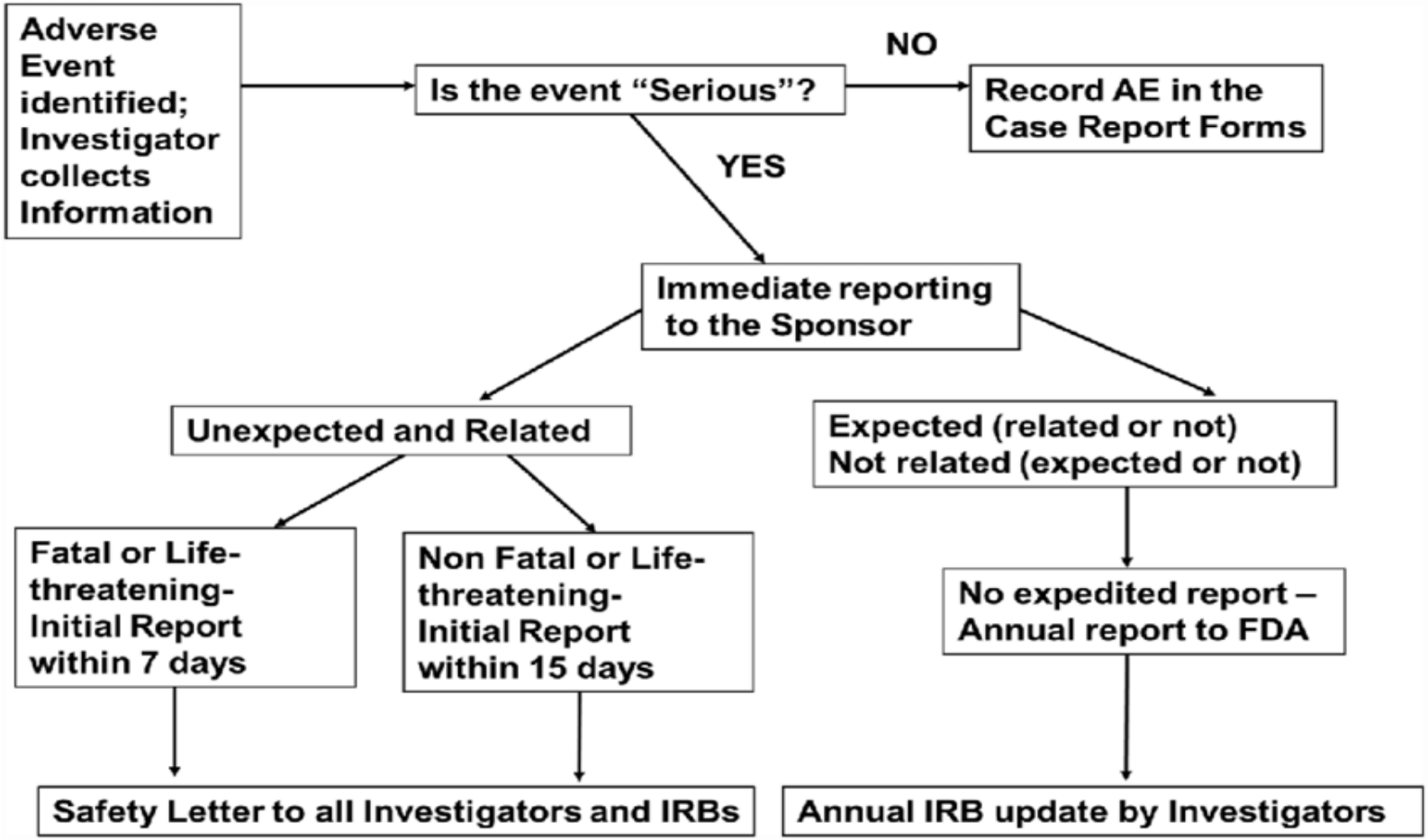
Conditional/ Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed Or additional data under examination

	Yes	No	Don't know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was given?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
4. Did the adverse reaction appear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could 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 toxic concentrations?	+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 drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

The total score calculated from this table defines the category as:

- POSSIBLY : Total score 1-4
- PROBABLY: Total score 5-8
- DEFINITELY: Total score >9


Adverse Event identified; Investigator collects Information
Is the event "Serious"?
NO
Record AE in the Case Report Forms
YES
Immediate reporting to the Sponsor
Unexpected and Related
Expected (related or not)
Not related (expected or not)
Fatal or Life-threatening- Initial Report within 7 days
Non Fatal or Life-threatening- Initial Report within 15 days
No expedited report – Annual report to FDA
Safety Letter to all Investigators and IRBs
Annual IRB update by Investigators

Prevention

- Avoid inappropriate use
- Appropriate dose, frequency of drug administration and duration of treatment
- Previous history and ongoing drug intake
- Past history of drug allergy
- Possible drug drug interaction before prescribing or dispensing or administering drugs
- If needed, do laboratory investigations

Treatment: Early identification of ADR and prompt treatment

- Withhold or withdraw the suspected drug
- Assess the ADR is requiring primary care or emergency care
- Maintain A - B - C
- Treatment of poisoning

SUMMARY

THANK YOU