

# **UNIT-IV**

## **SAFETY DATA GENERATION**



**CENTURION**  
**UNIVERSITY**  
*Shaping Lives...  
Empowering Communities!*

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- **Pre clinical phase**
  - **Clinical phase**
- **Post approval phase (PMS)**

# Drug safety and pharmacovigilance

- Modern drug safety and pharmacovigilance dates back to thalidomide disaster
- Amendment of Federal Food, Drug and Cosmetic Act
- Physicians were instructed through a federal program (MedWatch) to report any ADR to the FDA.
- The Committee on Safety of Drugs (CSD) was formed in UK in 1963
- Yellow card system was introduced in 1964
- An international data base was established in Geneva in 1971

# Drugs withdrawn for safety reasons

Drugs	Reason for withdrawal
Practalol	Oculomcocutaneous reaction
Troglitazone	Liver damage
Cerivastatin	Skeletal muscle damage
Rofecoxib	Myocardial infarction
Furazolidine	Cancer
Analgin	Bone marrow depression

Pre-clinical  
phase

- *In-vitro*
- *In-vivo*

Clinical  
phase

- Humans
- Case report form (Sponsor)

Post approval  
phase

- Marketing authorization holders
- Periodic safety reports

# Safety data generation

- Pre-clinical phase
- Clinical phase
- Post approval phase

# Pre-clinical phase/development

- *In-vitro* and *in-vivo* studies
- Exploratory toxicology: These studies provide a rough quantitative estimate of toxicity of the compound when given acutely or repeatedly over a short period. It provides an indication of the main organs and physiological systems involved.
- Regulatory toxicology: These studies are performed to GLP standards and comprise those that are required by regulatory authorities. Also performed to support an application for marketing approval.

# Exploratory toxicology

*In-vitro* and *In-vivo* screening for:

- Mutagenicity
- Cytotoxicity
- Immunotoxicity
- Hepatotoxicity
- Embryotoxicity
- *In-silico* screening



# Regulatory toxicology

- Safety pharmacology
- *In-vitro and In-vivo studies*
- *GLP guidelines*
- 28 day repeat dose toxicity and recovery in 2 species
- 3-12 month chronic toxicity in 2 species
- Reproductive toxicity in 1 species
- 24 month carcinogenicity in 2 species

# Safety pharmacology

- Core battery of tests
- Follow up tests
- Supplementary tests

# Core battery of tests

System	Tests
CNS	Motor activity Behavioral changes Body temperature Coordination
CVS	Blood pressure Heart rate ECG changes
Respiratory system	Respiratory rates Tidal volume

# Follow-up tests

System	Tests
CNS	Tests on learning and memory Tests for motor function Tests for visual function
CVS	Cardiac output Ventricular contractility Vascular resistance Regional blood flow
Respiratory system	Airways resistance Pulmonary arterial pressure Blood gases

# Supplementary tests

System	Tests
Renal function	Urine volume, pH Proteinuria Blood urea, creatinine
ANS	CVS, GIT and respiratory responses to agonists, stimulation of autonomic nerves
GIT	Gastric secretion, pH GI motility, GI transit time

# Safety data in clinical trials

- Report serious adverse events
- Conduct subject follow up visits
- Ensure subject compliance
- Continue communication

# Safety monitoring



# Adverse Events

Unexpected  
AE

Common

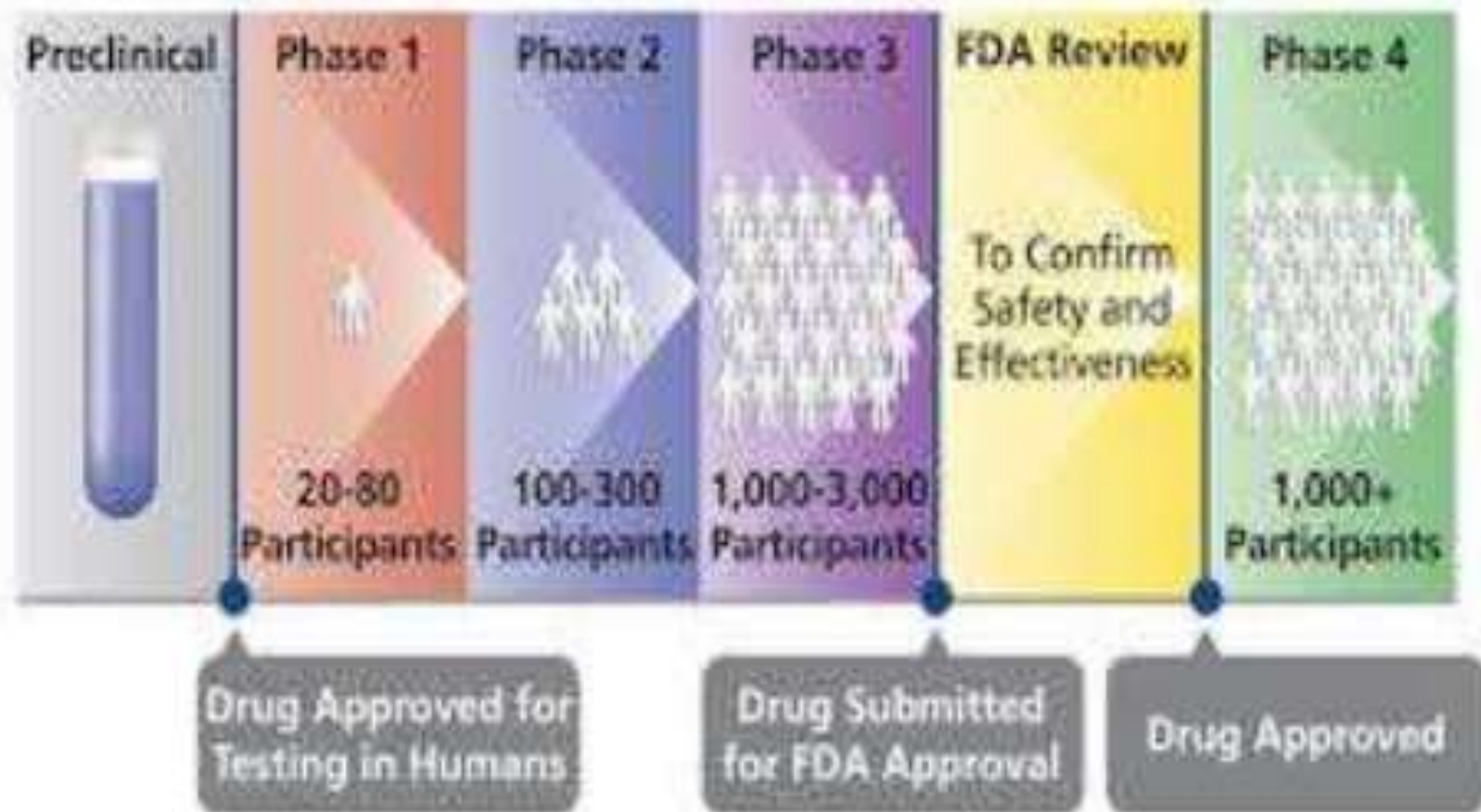
Abnormal  
Lab Report

Rare and  
Special

Serious



# Clinical Trials



## Clinical Trials

1 Year

20-100 People  
1-2 Years

100 - 300 People  
1-2 Years

1,000- 3,000 People  
2-3 Years

1-2 Years

Pre-Clinical  
Animal Studies

Phase 1  
Safety

Phase 2  
Efficacy  
Safety

Phase 3  
Efficacy  
Safety

FDA Review  
& Approval

Pharmacological profile  
Administration route  
Drug interactions

## Adverse Event / Experience

- Any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related
  - sign, symptom, or disease
  - abnormal lab, imaging, ECG, etc
  - worsening of the above
  - constellation of the above

# Adverse Events

- Any untoward medical occurrence observed during treatment with a pharmaceutical product which does not necessarily have a causal relationship with the treatment.
- Any new clinical experience
- Adverse outcome that occurs after use of a drug
- May or may not be linked to the use of a drug
- Examples: cardiac arrhythmia after discontinuing atenolol, abnormal ECG report, abnormal lab report

# Sources of safety information and evaluation

- Spontaneous ADR reporting schemes
- Data from clinical and epidemiological studies
- Data from pharmaceutical companies
- Journals data source
- News bulletins
- Data available with regulatory authorities
- Safety profile of other drugs of similar class/type
- Data from pre-clinical studies

# Sources of safety information and evaluation

- **Non-clinical information**
- Chemical structure, class adverse effects, class actions
- *In-vitro* studies report
- Data from toxicology studies in animals (carcinogenicity, hepatotoxicity, cardiotoxicity, renal toxicity, embryotoxicity)

# Serious adverse event

- Any untoward medical occurrence that at any dose results in death
- Life threatening
- Requires inpatient hospitalization
- Prolongation of existing hospitalization
- Results in persistent or significant disability
- Results in congenital birth defect
- Requires intervention to prevent permanent damage

# Unexpected adverse event

- The nature or severity of which is not consistent with the applicable product information
- Not consistent with the risk information described in general investigational plan of investigation brochure
- Not listed at the specificity or severity observed
- Not listed in investigator's brochure



# Advers drug reaction

- The nature or severity of which is not consistent with the applicable product information
- Not consistent with the risk information described in general investigational plan of investigation brochure
- Not listed at the specificity or severity observed
- Not listed in investigator's brochure

# Investigational new drug safety reporting requirement

- Any unexpected or life threatening adverse events must be reported more rapidly to FDA
- Any unexpected or life threatening adverse events must be reported within 7 days
- A major safety finding from a newly completed animal study such as carcinogenicity
- A significant hazard to the patient population such as lack of efficacy with a medicinal product used in treating life threatening diseases

# Adverse event reporting time line

- Death and life threatening-serious adverse events must be reported must be reported by the sponsor to the regulatory authority within 7 days
- Any other unexpected AEs that are neither fatal nor life threatening should be reported within 15 days

# Post marketing safety

- Post marketing surveillance
- Clinical trials are conducted for a limited period
- Small number of participants are involved in clinical trials
- No real life setting in clinical trials
- PMS can refine, confirm or deny the safety of the drugs

# Post marketing Reports

- Periodic safety update reports
- PSUR process
- Intake of ADR information
- Data retrieval
- Data analysis
- In India PSURs should be submitted every 6 months for first two years and annually for subsequent 2 years

## Postmarketing Safety...

- Approaches to monitor the safety of licensed drugs:
  - Spontaneous reporting databases,
  - Prescription event monitoring,
  - Electronic health records,
  - Patient registries,
  - Nonclinical studies,
  - Observational studies and
  - Record linkage between health databases
- These data are reviewed to highlight potential safety concerns in a process known as **data mining**

## Postmarketing Safety...

- For post-market safety evaluations, data sources are
- Product's preapproval safety profile,
- Current FDA-approved label,
- Reports made to FDA Adverse Event Reporting System (FAERS),
- Reports made to Vaccine Adverse Event Reporting System (VAERS),
- Manufacturer submitted periodic safety update reports (PSURs),
- Medical literature,
- Drug utilization databases &
- Data from post-approval clinical trials & other studies, when applicable

# Postmarketing Reports

- For ensuring drug safety on long term & on a wider population, regulatory authorities ask the marketing authorization holders (MAH) for
  - Reporting of AEs &
  - Periodic submission of safety reports
- For serious & unexpected AEs, FDA recommends reports to be submitted **within 15 calendar days** either foreign or domestic
- **Follow up to 15-day alert reports** should be submitted **within 15 calendar days**



# Post marketing reports

- For ensuring safety on long term and on a wider population
- Regularly authorities ask the marketing authorization holders (MAH) for reporting of AEs and submission of periodic safety reports
- For serious and unexpected AEs, FDA recommends reports to be submitted within 15 days
- Follow up to 15 day alert reports should be submitted within 15 days