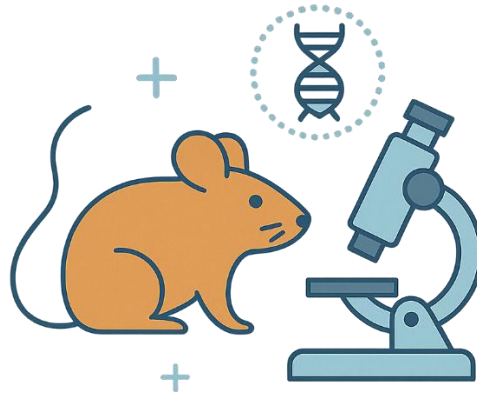


Safety data generation

Preclinical Phase (Non-clinical Studies)

Purpose:

- To evaluate the safety profile of a new drug before it is tested in humans.



PRECLINICAL PHASE

Types of Studies:



Types of Toxicology Studies

— In Vitro Testing (Lab-based)

— In Vivo Testing (Animal-based)

A. In Vitro Testing (Lab-based)

- **Cell culture assays:** Determine cytotoxicity (how toxic the compound is to cells).
- **Mechanism of action studies:** Understand how the compound interacts with biological targets.
- **Genotoxicity tests:**
 - *Ames test:* Detects DNA mutations in bacteria.
 - *Micronucleus assay:* Detects chromosomal damage in mammalian cells.

B. In Vivo Testing (Animal-based)

1. Single-dose (acute) toxicity studies:

- Conducted in **two species (usually rodent and non-rodent)**.
- Measures LD₅₀ (lethal dose that kills 50% of animals).
- Observes signs like tremors, seizures, death, etc.

2. Repeated-dose (subacute/chronic) toxicity studies:

- Drug given daily for weeks to months.

- Helps understand cumulative toxic effects on organs (liver, kidney, etc.).

3. Carcinogenicity (long-term cancer risk):

- Often performed in mice and rats for up to **2 years**.

4. Reproductive and developmental toxicity:

- Assesses effects on fertility, embryo-fetal development, and teratogenicity (birth defects).

5. Toxicokinetics:

- Measures absorption, distribution, metabolism, excretion (ADME) in animals.
- Assists in dose extrapolation to humans.

6. Safety Pharmacology:

- Evaluates effects on critical systems:
 - CNS (Central Nervous System)
 - CVS (Cardiovascular System)
 - Respiratory System
- HERG assay for QT prolongation (heart rhythm issue).

Role in Pharmacovigilance:

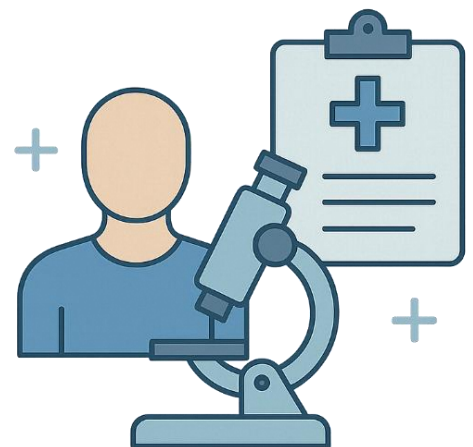
- Identifies potential risks that can be monitored in later phases.
- Helps in selecting safe starting doses for human trials.
- Provides the first safety signal detection opportunity.
- Although pharmacovigilance is mainly concerned with human data, non-clinical safety data sets the foundation for risk assessment.

Clinical Phase (Human Trials)

- Clinical trials are conducted in four phases (I–IV), but for safety data generation, Phases I–III are especially relevant before market approval.

Phase 1: First-in-Human Safety Studies

- **Subjects:** 20–100 healthy volunteers (sometimes patients if drug is too toxic).
- **Goal:** Safety, tolerability, PK/PD (pharmacokinetics/pharmacodynamics).
- **Key Safety Data Collected:**
 - Adverse Events (AEs)



CLINICAL PHASE

- Serious Adverse Events (SAEs)
- Vital signs, ECGs, lab tests
- Dose escalation design: start low, increase until MTD (maximum tolerated dose)

Phase 2: Safety in Patients with the Disease

- **Subjects:** 100–300 patients with the target disease.
- **Goal:** Preliminary efficacy + continued safety monitoring.
- **Key Safety Assessments:**
 - Compare frequency/severity of AEs vs placebo or other treatments.
 - Identify dose-related safety issues.
 - Establish dose-response relationship.

Phase 3: Large-Scale Confirmation

- **Subjects:** 1000–3000 patients (sometimes more).
- **Goal:** Confirm efficacy and safety in larger, more diverse populations.
- **Safety Monitoring:**
 - Rigorous adverse event reporting systems.
 - Routine lab monitoring, ECGs, imaging.
 - Data Safety Monitoring Boards (DSMBs) review data periodically.
 - All SAEs are reported to regulatory authorities within specific timelines.
- **Outcome:**
 - Benefit-risk profile finalized.
 - Forms the core of the New Drug Application (NDA) or Marketing Authorization Application (MAA).

Role in Pharmacovigilance:

- Safety data collected here is used to create the Investigator’s Brochure, Risk Management Plan (RMP), and labeling information.
- Signals from this phase are critical in understanding predictable and dose-related adverse effects.

Post-Approval Phase (Post-Marketing Surveillance / PMS) Also Known As: Phase IV

Purpose:

- To continue safety monitoring after the drug has been approved and marketed to the general population.



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