DEPTH OF BIOLOGY

Unit-1

Basic definition and types of toxicology (general, mechanistic, regulatory and descriptive)

Regulatory guidelines for conducting toxicity studies OECD, ICH, EPA and Schedule Y

OECD principles of Good laboratory practice (GLP)

History, concept and its importance in drug development

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Basic definition and types of toxicology

[general, mechanistic, regulatory and descriptive]

The word "toxicology" comes from the Greek words:
Toxikon = poison (originally meaning arrow poison)
Logos = study/science

Toxicology is the branch of science that deals with the study of adverse effects of chemicals or physical agents on living organisms.

It integrates principles from pharmacology, chemistry, biology, and medicine to understand:
The nature of toxic substances
The mechanism of their harmful effects
Detection, prevention, and treatment of toxicity

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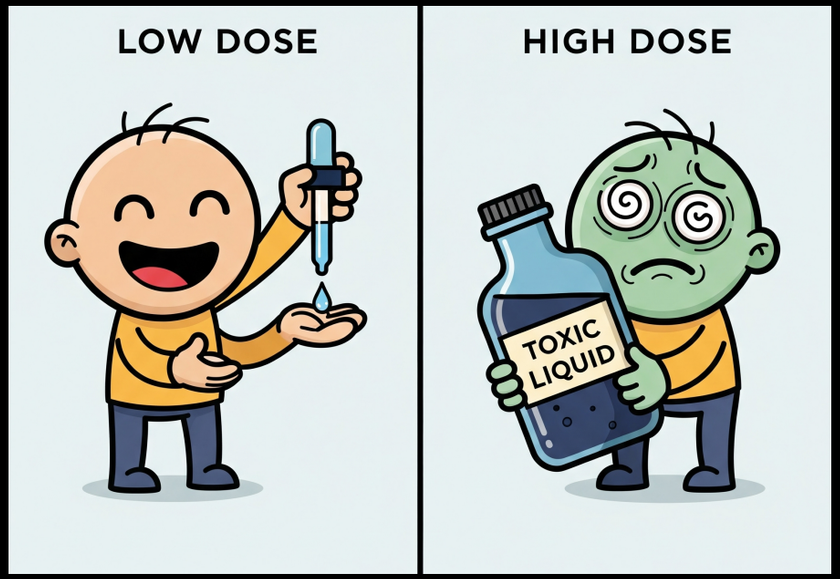
1. General Toxicology

General toxicology - is the broad study of the harmful effects of chemical, physical, or biological agents on living organisms, including the nature of the toxic effects, their mechanisms, dose-response relationships, prevention, and treatment.

It is the basic branch of toxicology that studies:

Nature of poisons (what they are, where they come from)
Exposure (how poisons enter the body)
Dose-response relationship (how much is harmful)
Mechanism of action (how they damage the body)
Management & prevention of poisoning.



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Example Cases-

Lead exposure from contaminated water → anemia, neurotoxicity.

CO poisoning in enclosed garage → hypoxia.

Organophosphate pesticide ingestion → cholinergic crisis.

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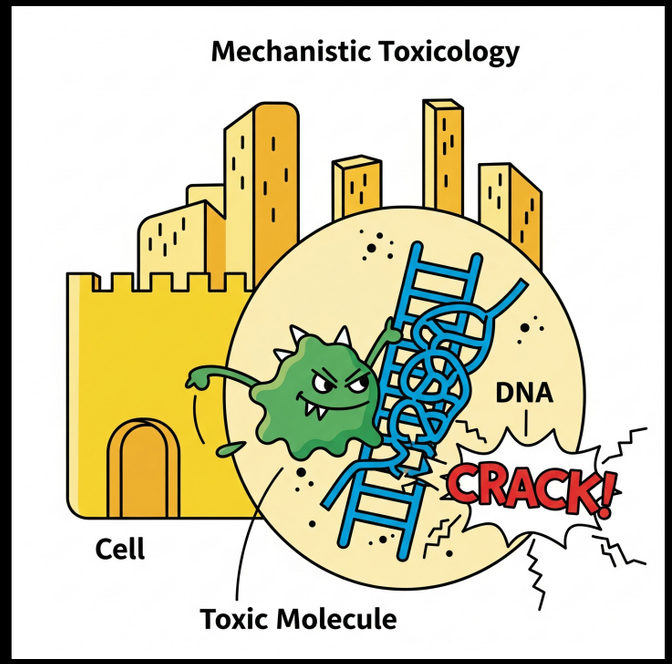
2. Mechanistic Toxicology – It is the branch of toxicology that studies how poisons work inside the body — from the moment they enter, to how they damage cells, and why they cause certain symptoms.

Think of it as: "What exactly does the poison do inside you?"

Why Important ?

Helps scientists make safer medicines.
Helps doctors choose the right antidote.
Helps governments set safety limits for chemicals.



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Steps in Mechanistic Toxicology

-Poison enters the body (by eating, breathing, touching, injection).

-It finds its target inside the body (like enzymes, receptors, or DNA).

-It changes how the target works (blocks it, damages it, over-activates it).

-Cells stop working properly (less energy, broken cell membranes, damaged proteins/DNA).
-Organs get damaged (liver, brain, kidney, etc.).
-You get symptoms (headache, vomiting, coma, death).
-Body tries to repair (antioxidants, DNA repair, enzyme recovery).
-If repair fails → permanent damage or death.

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Examples-

Cyanide → Blocks a key enzyme in cells (cytochrome oxidase) → Cells can't use oxygen → You suffocate at the cellular level.

Organophosphate pesticide → Blocks an enzyme (acetylcholinesterase) → Nerves send too many signals → Muscle twitching, breathing problems.

Paracetamol overdose → Makes a harmful chemical (NAPQI) → Damages liver cells → Liver failure.

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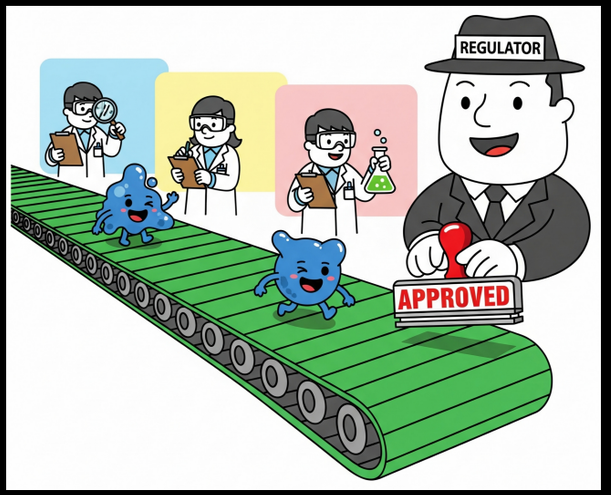
3. Regulatory Toxicology- It is the part of toxicology that uses scientific data to make rules and laws about how much of a chemical, drug, or pollutant is safe for people and the environment.



Think of it as:

📚 Science + ⚖️ Law = Safety Rules

Why It Exists

To protect people from harmful substances

To set limits for chemicals in food, water, medicines, air, etc.

To approve safe products and ban unsafe ones

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What They Do -

Find dangerous chemicals (hazard identification)
Check how much is harmful (dose-response)
See how much people are exposed to (exposure assessment)
Decide safe limits
Make rules — e.g., "This much is safe, more than this is banned"

Examples

Deciding how much pesticide can remain in vegetables (MRL - maximum residue limit)
Approving a new medicine only if it's safe
Banning a chemical that causes cancer

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4. Descriptive Toxicology

It is the part of toxicology that describes what a chemical does to living things by testing and observing its harmful effects.

Main Features-

Focuses on testing chemicals (on cells, animals, or humans)
Measures toxicity → how poisonous a substance is
Does not study the exact mechanism — that's for mechanistic toxicology
Data collected here is used by regulatory toxicology to set safety standards

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What They Do-

Give different doses of the chemical to test animals or cell cultures

Record the harmful effects

Find the LD_{50} (dose that kills 50% of test animals)

Study short-term and long-term toxicity

Compare toxicity of different chemicals

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Example-

Testing a new pesticide in rats to find:

Acute toxicity (short-term harm)
Chronic toxicity (long-term harm)
Recording effects like weight loss, organ damage, or death

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1. Guidelines for conducting toxicity studies OECD

They make international rules for testing chemicals, drugs, pesticides, etc., to check if they are safe.

If a study follows OECD rules, all member countries accept it (no need to repeat tests).

Developed OECD Test Guidelines (TGs) for the safety testing of chemicals, including drugs, pesticides, cosmetics, industrial chemicals, and environmental pollutants.

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Why OECD Guidelines are Necessary in Toxicology-

International Acceptance of Data

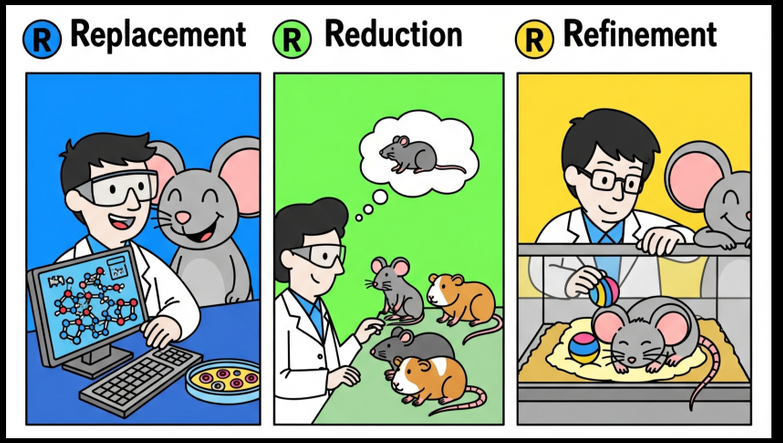
If a toxicity study follows OECD rules, it is accepted by all member countries.

Avoids repeating the same test in different countries → saves time and money.

Standardisation

Uses the same testing methods worldwide.

Results from different labs are comparable and reliable.



Animal Welfare

Promotes the 3Rs principle (Reduce, Refine, Replace animals in testing).

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Quality Assurance

Must follow Good Laboratory Practice (GLP) → ensures accurate, trustworthy results.

Regulatory Approval

Required for safety evaluation before a product (drug, pesticide, chemical) can be marketed.

Avoids Duplication

One properly conducted study can be used in many countries for registration.

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Important OECD Toxicity Tests & Numbers

Test Type	OECD Guideline No.	What it Checks
Acute oral toxicity	TG 420, 423, 425	Harm after single oral dose
Acute dermal toxicity	TG 402	Harm after skin exposure
Acute inhalation toxicity	TG 403, 436	Harm after breathing it in
Skin irritation	TG 404	Damages skin or not
Eye irritation	TG 405	Damages eyes or not
Skin sensitisation	TG 406, 429	Allergic skin reaction
Repeated dose (28 days)	TG 407	Harm from repeated exposure

2. ICH Guidelines – Toxicology

Think of ICH as a group of countries sitting at one table (USA, Europe, Japan, etc.) deciding:
"Let's all follow the same rules for drug testing so we don't waste time doing the same tests again in each country."

What is ICH?
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Makes global rules for drug development so USA, Europe, Japan, and other members follow the same standards.

Ensures safety, quality, and efficacy of medicines.

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If every country had different rules, a company would have to repeat animal tests again and again — more time, more cost, more animals used.

ICH says:
"One proper safety test = accepted everywhere."
This saves time and gets safe medicines to patients faster.

Why ICH Guidelines for Toxicity?

To make sure non-clinical safety tests (animal or lab tests) are reliable before human trials.
Avoid duplication of tests in different countries.

Speed up approval process globally.

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How does it work in Toxicology?

Before a new medicine is given to people, ICH says:

Test in animals first to check for harmful effects.

Follow specific steps — short-term, long-term, special tests.

Match test length to human use (e.g., if a person will take it for 1 month, animal test is also about 1 month).

Record everything properly so data can be trusted worldwide.

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Code	What it checks	Simple Meaning
M3(R2)	General rules for all toxicity studies	The “roadmap” for when & how to test
S1	Carcinogenicity	Does the drug cause cancer?
S2(R1)	Genotoxicity	Can it damage DNA?
S3	Toxicokinetics	How the body handles the drug
S4	Chronic toxicity	Effects after long-term use

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S5	Reproductive toxicity	Harm to pregnancy or fertility
S6	Biotech product safety	Special tests for biologics like antibodies
S7	Safety pharmacology	Effects on heart, brain, lungs
S8	Immunotoxicity	Effects on the immune system
S9	Anticancer drugs	Special rules for chemotherapy safety
S10	Photosafety	Harm from sunlight exposure
S11	Pediatric safety	Testing for children’s medicines

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1. EPA Guidelines (Environmental Protection Agency – USA)-

Purpose:
To make sure chemicals, pesticides, and industrial products are safe for humans, animals, and the environment before they are approved for use in the USA

Why EPA guidelines are important-

To protect public health and environment from harmful chemicals.
To make testing methods uniform across all companies.
To ensure scientific validity of toxicity data.
To prevent disasters like poisoning, cancer outbreaks, or ecosystem damage.

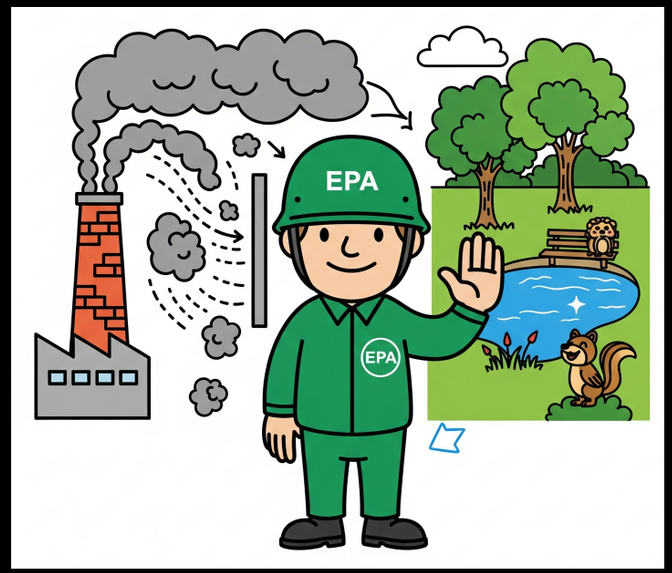
Types of Toxicity Studies Under EPA-

EPA mainly follows the Toxic Substances Control Act (TSCA) and FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act) testing requirements.

1. Acute Toxicity Studies

Purpose: Measure harmful effects from single short-term exposure.
Animals used: Rats, mice, rabbits.

End points measured:
LD_{50} (dose killing 50% animals)
Skin irritation
Eye irritation
Inhalation toxicity
Duration: Usually 14 days observation after single dose.



2. Sub-chronic Toxicity Studies-

Purpose: See effects of repeated exposure for intermediate duration.
Duration: Around 90 days.
Animals: Rodents and non-rodents.

Parameters studied:
Body weight
Organ weight
Blood tests (hematology, biochemistry)
Histopathology (microscopic organ changes)

3. Chronic Toxicity Studies-

Purpose: Identify long-term health effects including cancer risk.
Duration: 1–2 years.
Animals: Rodents (2 years), dogs/monkeys (1 year).

Checks:
Tumor formation
Organ degeneration
Lifespan effects

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4. Reproductive & Developmental Toxicity-

Purpose: Check if a chemical affects fertility, pregnancy, and offspring.
Tests include:
Fertility studies in male & female animals.
Teratology (birth defects) studies.
Perinatal and postnatal studies.

5. Mutagenicity & Genotoxicity-

Purpose: See if the chemical damages DNA or causes genetic mutations.
Common tests:
Ames test (bacteria mutation test)
Chromosomal aberration test
Micronucleus assay

6. Ecotoxicity Studies-

Purpose: Assess harm to plants and wildlife.
Tests include:
Acute toxicity to fish (LC_{50})
Effects on birds, bees, and earthworms
Plant growth inhibition tests
Algal toxicity tests

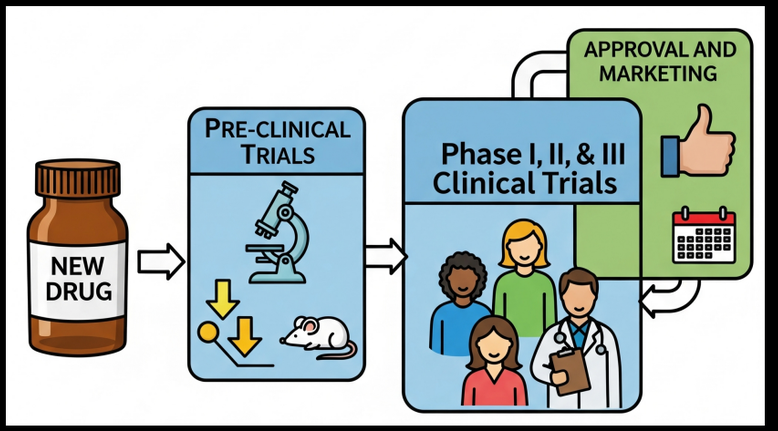
EPA Study Requirements-

Good Laboratory Practices (GLP) must be followed.
Use at least two animal species (one rodent, one non-rodent) when needed.
Studies should be scientifically valid and ethically approved.
Data should allow for risk assessment in humans and environment.

Schedule Y – Regulatory Guidelines for Conducting Toxicity Studies (India)

1. What is Schedule Y-

Part of: Drugs and Cosmetics Rules, 1945 (India).
Purpose: Sets rules for clinical trials, preclinical studies (including toxicity studies), and drug approvals in India.
Issued by: Central Drugs Standard Control Organization (CDSCO).



2. Role in Toxicology-

Schedule Y tells us what toxicity studies must be done before a new drug can be tested on humans in India.

3. Main Toxicity Study Requirements under Schedule Y-

Stage	Type of Study	Purpose	Example
Preclinical	**Acute toxicity**	Find lethal dose (LD_{50}) & immediate toxic effects	Single high dose test in 2 animal species
	Repeated dose (sub-acute/sub-chronic/chronic)	See effects of long-term exposure	28-day, 90-day, 180-day animal studies
	Genotoxicity	Detect DNA damage/mutations	Ames test, chromosomal aberration test
	Reproductive & developmental toxicity	Effects on fertility, pregnancy, fetus	Multi-generation animal studies
	Carcinogenicity	Detect cancer-causing potential	2-year rat/mouse studies

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4. Key Rules in Schedule Y for Toxicology Studies-

Must follow Good Laboratory Practices (GLP).
Two animal species required (one rodent, one non-rodent).
Toxicity studies must be completed before starting clinical trials.
Testing must follow ethical guidelines (animal welfare).
Data should be in a standard format for regulatory submission.

5. Why Schedule Y is Important-

Protects human volunteers in trials.
Ensures drugs are safe & effective before approval.
Makes Indian regulations align with global standards (OECD/ICH).

OECD Principles of Good Laboratory Practice (GLP)

1. What is GLP?

Full form: Good Laboratory Practice

Issued by: OECD (Organisation for Economic Co-operation and Development).

Purpose:

Ensure quality, integrity, reliability, and reproducibility of laboratory data.

Make toxicity study results acceptable worldwide (avoid repeating animal studies in different countries).

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2. Why GLP is important in toxicology?

Because toxicity data is used for human safety decisions. If data is poor or unreliable, a harmful drug or chemical could be approved. GLP ensures:

Proper planning

Proper documentation

Traceable, verifiable results

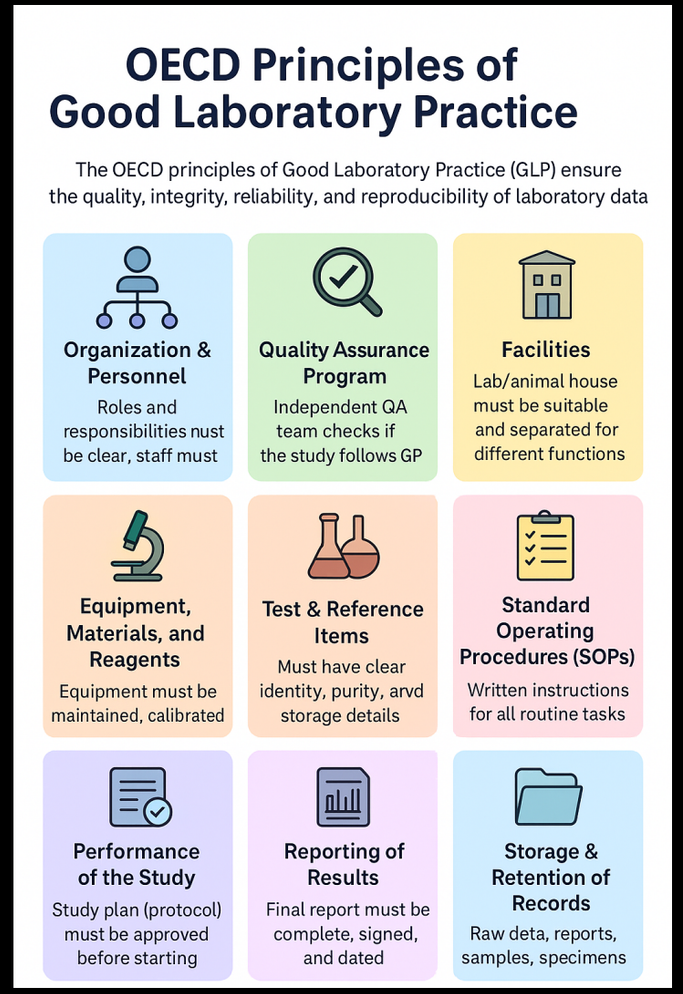
Benefits of OECD GLP-

International acceptance of data (no duplication of studies).

Protects animal welfare by avoiding repeated tests.

Improves trust in safety assessments.

Helps regulatory authorities make correct decisions.



3. OECD GLP Principles – Main Points

Principle	Meaning (Simple)	Example in Toxicology Study
1. Organization & Personnel	Roles and responsibilities must be clear; staff must be qualified.	Toxicologist, animal caretaker, study director all have defined duties.
2. Quality Assurance Program	Independent QA team checks if the study follows GLP.	QA auditor verifies animal dosing records.
3. Facilities	Lab/animal house must be suitable and separated for different functions.	Quarantine room separate from dosing room.
4. Equipment, Materials, and Reagents	Equipment must be maintained, calibrated; chemicals labeled with expiry.	Analytical balance calibrated before weighing.

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5. Test & Reference Items	Must have clear identity, purity, and storage details.	New drug sample stored at correct temperature.
6. Standard Operating Procedures (SOPs)	Written instructions for all routine tasks.	SOP for blood collection in toxicity study.
7. Performance of the Study	Study plan (protocol) must be approved before starting.	Detailed schedule for 90-day repeated dose study.
8. Reporting of Results	Final report must be complete, signed, and dated.	Report includes raw data, results, and interpretation.
9. Storage & Retention of Records	Raw data, reports, samples, and specimens must be archived for future reference.	Tissue slides stored for 5 years for review.

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History, concept and its importance in drug development

1. History of Toxicology

Ancient Period

Humans knew certain plants, minerals, and animal venoms could harm or kill.

Early use of poisons in hunting, warfare, and executions (e.g., hemlock, arsenic, snake venom).

Paracelsus (1493–1541) – Father of Toxicology – introduced the idea:

"All things are poison, and nothing is without poison; only the dose makes a thing not a poison."

Pre-modern Era (17th–19th Century)

Development of analytical chemistry → detection of poisons in tissues (forensic toxicology).

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Pre-modern Era (17th–19th Century)

Development of analytical chemistry → detection of poisons in tissues (forensic toxicology).

Recognition of occupational poisonings (e.g., lead toxicity in miners).

Modern Era (20th Century onwards)

Growth of industrial chemicals, drugs, pesticides → need for safety testing.

Formation of OECD, WHO, US FDA, ICH guidelines for toxicity testing.

Advances in cell biology, molecular biology, and analytical methods improved understanding of toxic mechanisms.

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Concept of Toxicology-

Definition: Science that studies harmful effects of chemical, physical, or biological agents on living organisms.

In drug development, toxicology:

Identifies potential harmful effects of a new drug.

Explains how these effects occur (mechanism).

Determines safe dose ranges.

Includes different types-

General Toxicology – broad study of harmful effects.

Descriptive Toxicology – animal/in vitro testing to find toxic effects.

Mechanistic Toxicology – how the drug causes harm.

Regulatory Toxicology – applying safety standards.

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3. Importance in Drug Development-

-Target Identification: Helps find molecular targets (receptors, enzymes) for drugs.
-Mechanism Understanding: Explains how drugs produce desired effects and possible side effects.
-Safety & Efficacy: Determines therapeutic window (safe and effective dose range).
-Toxicity Reduction: Minimizes harmful effects before human use.
-Optimizing Drug Delivery: Guides choice of dosage form and route (oral, IV, topical).
-Regulatory Approval: Provides scientific data required for drug licensing.
-Personalized Medicine: Uses patient-specific data for tailored drug therapy.
-Innovation in Treatment: Leads to new classes of drugs for previously untreatable conditions.

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Tests include:

Acute Toxicity – single high-dose effect.

Sub-chronic & Chronic Toxicity – repeated dosing over weeks/months.

Carcinogenicity – cancer-causing potential.

Reproductive & Developmental Toxicity – effects on fertility and fetus.

Genotoxicity – DNA damage potential.

Determines NOAEL (No Observed Adverse Effect Level) → helps set safe starting doses for clinical trials.

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b) Clinical Trials

Monitors adverse drug reactions in humans.

Adjusts dose or formulation if toxicity observed.

c) Post-Marketing Surveillance

Detects rare or long-term toxic effects not seen in trials.

Why It's Important

Patient Safety – prevents harmful drugs from reaching market.

Regulatory Approval – required by authorities (FDA, EMA, CDSCO) before clinical trials.

Risk–Benefit Analysis – ensures the benefit outweighs the risk.

Design of Safer Drugs – understanding toxicity mechanism helps in making safer molecules.

Ethical Responsibility – protects human and animal health.