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Unit-4

IND enabling studies (IND studies)- Definition of IND, importance of IND, industry perspective, list of studies needed for IND submission.

Safety pharmacology studies- origin, concepts and importance of safety pharmacology.

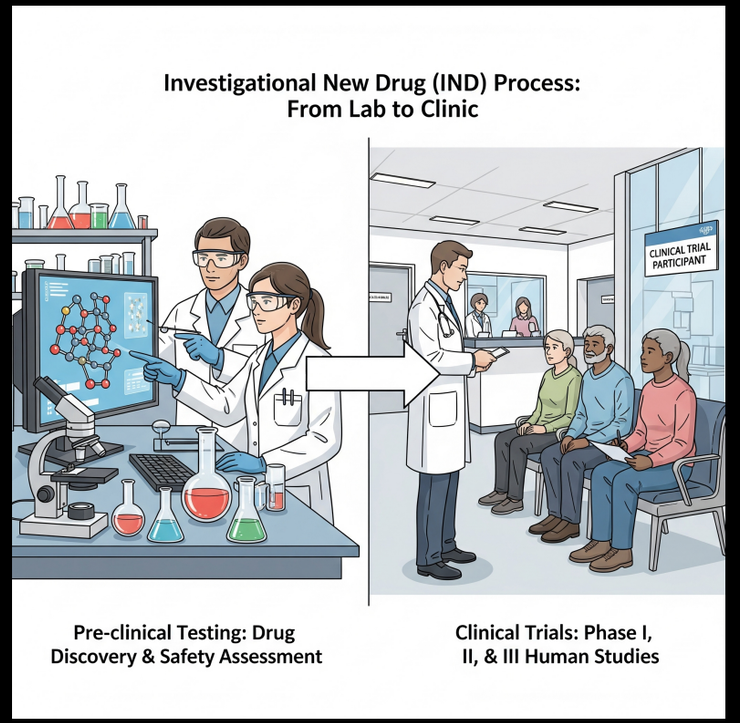
Tier1 - CVS, CNS and respiratory safety pharmacology, HERG assay. Tier2- GI, renal and other studies

IND enabling studies (IND studies)

Investigational New Drug-

IND-enabling studies are the preclinical safety and toxicity tests done before a new drug can be given to humans.

They generate the data needed to submit an Investigational New Drug (IND) application to regulatory agencies (like the US FDA).



IND-enabling studies (Investigational New Drug-enabling studies) are a set of non-clinical (animal and in vitro) experiments required by regulatory authorities to demonstrate:

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1. Safety – to identify potential toxic effects of the drug.

2. Pharmacology – to show the drug's mechanism of action and activity.

3. Pharmacokinetics (ADME studies) – absorption, distribution, metabolism, and excretion.

4. Toxicology – acute, subacute, and chronic toxicity in at least two species (rodent + non-rodent).

5. Genotoxicity – studies like Ames test, micronucleus test, chromosomal aberration studies.

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6. Reproductive & developmental toxicity – (if relevant).

7. Carcinogenicity – only if long-term use is expected.

8. Safety pharmacology – effects on vital organ systems (CNS, cardiovascular, respiratory).

Importance of IND (Investigational New Drug)

1. Legal Importance

IND is permission from the regulatory authority (like FDA in the US, CDSCO in India) to test a new drug in humans.

Without IND, giving the drug to people is illegal.

2. Patient Safety

Ensures that the drug has been tested in animals first.

Protects humans from unsafe drugs by checking toxicology and safety data.

Requires informed consent and ethics committee (IRB) approval before trials.

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3. Scientific Importance

Provides all details about the drug:

How it works (pharmacology)

How it is absorbed, distributed, metabolized, excreted (pharmacokinetics)

Side effects seen in animals (toxicology)

How it is manufactured and checked for quality (CMC data).

Ensures the drug is of good quality and consistent.

4. Drug Development Importance

First step to human trials → starts Phase I clinical trial.

Builds the foundation for later approval (NDA – New Drug Application).

Prevents unsafe or poor-quality drugs from wasting time and money in clinical trials.

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5. Business & Research Importance

Makes the project credible for investors, partners, and research institutes.

Provides documentation that supports patent protection and innovation.

Increases chances of successful drug development.

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List of Studies Needed for IND Submission

1. Pharmacology Studies-

Primary pharmacodynamics

Secondary pharmacodynamics

Safety pharmacology (effects on vital systems – CNS, cardiovascular, respiratory)

2. Pharmacokinetics (ADME)

Absorption

Distribution

Metabolism

Excretion

Bioavailability & dose-response

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3. Toxicology Studies-

Acute toxicity (single-dose)
Subacute/subchronic repeated-dose toxicity
Genotoxicity (Ames test, chromosomal aberration, micronucleus)
Reproductive toxicity (fertility, embryo-fetal development, teratogenicity)
Carcinogenicity (for chronic/long-term drugs)

4. Chemistry, Manufacturing, and Controls (CMC)-

Drug substance (structure, purity, stability)
Drug product (formulation, excipients, dosage form)
Manufacturing process & quality control
Stability studies.

5. Clinical Information-

Investigator's Brochure (IB)
Clinical trial protocol (Phase I plan)
Informed Consent Form (ICF)
Investigator qualifications & IRB approval

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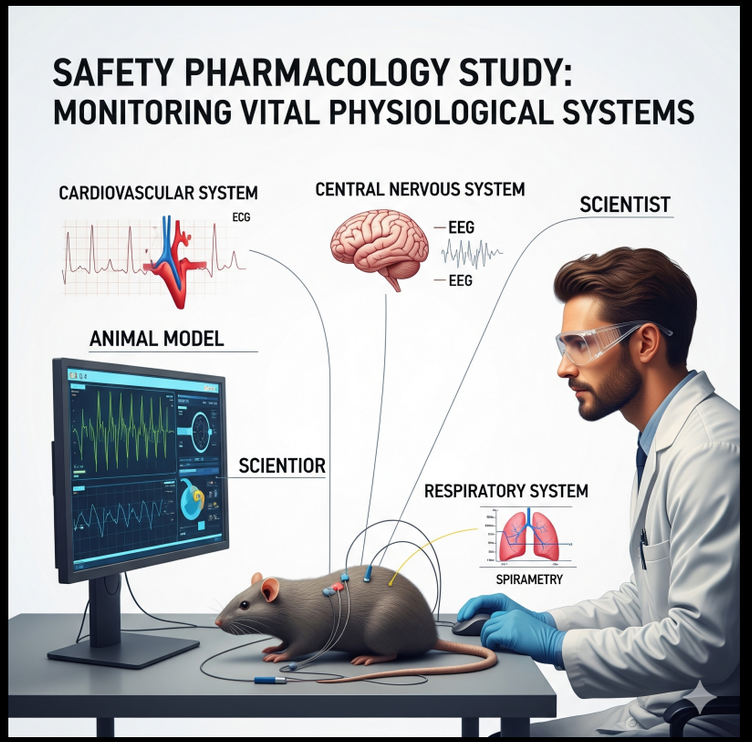
Safety pharmacology studies- origin, concepts and importance of safety pharmacology.

Safety pharmacology studies are non-clinical (preclinical) studies conducted to evaluate the potential undesirable pharmacodynamic effects of a new drug (on vital organ systems), at therapeutic and above-therapeutic doses.

These studies ensure that the drug does not harm the essential body functions.



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Origin

1. Before Safety Pharmacology (Pre-1990s)-

-Earlier, drug development mainly focused on:
-Toxicology studies (acute, subacute, chronic, reproductive, carcinogenicity).
-These measured structural and biochemical damage (organ toxicity, carcinogenesis).
-Pharmacodynamic safety was neglected → some drugs passed toxicology but later caused serious functional problems (e.g., arrhythmias, seizures, respiratory failure).

-Result → Drugs were withdrawn after marketing, leading to patient deaths.

2. Triggering Events-

Several drugs were withdrawn due to unexpected adverse effects on vital systems:

Thalidomide (1960s) – teratogenicity highlighted lack of proper preclinical testing.

Terfenadine (1990s) – antihistamine caused QT prolongation & fatal arrhythmias.
Cisapride, Astemizole – withdrawn due to cardiac safety issues.

These failures showed that classical toxicology was not enough; we needed functional (safety) studies on vital systems.

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3. Birth of Safety Pharmacology-

In the 1990s, regulatory agencies (FDA, EMA, etc.) recognized the need for standardized safety testing.

ICH (International Council for Harmonisation) published:

ICH S7A (2001): Guideline on Safety Pharmacology Studies for Human Pharmaceuticals → defined core battery studies (CNS, CVS, Respiratory).

ICH S7B (2005): Focused on cardiac safety & QT interval prolongation (torsades de pointes risk).

These guidelines made safety pharmacology mandatory for new drug approval.

4. Current Concept-

Now, safety pharmacology = functional toxicology → studying vital physiological functions rather than just organ damage.

Became a regulatory requirement worldwide → must be included in IND (Investigational New Drug) application before human trials.

Safety Pharmacology

Concept-
Safety pharmacology is the scientific discipline that evaluates the undesirable pharmacodynamic effects of a drug on vital physiological systems at therapeutic and higher doses.
It deals with functional safety (how the drug affects organ function), not just structural damage.

Introduced by ICH guidelines (S7A, 2001; S7B, 2005).
Focus is mainly on:
CNS (Central Nervous System)
CVS (Cardiovascular System)

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Importance-

1. Patient Safety

Detects life-threatening effects (arrhythmias, seizures, respiratory depression) before human trials.

Prevents tragedies like terfenadine (cardiac toxicity) or opioids (respiratory depression).

2. Regulatory Requirement

Mandatory part of IND submission.

Without safety pharmacology data, clinical trials cannot start.

Drug Development Success

Helps in early detection of risks → avoids late-stage drug failures.

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Determines Safe Dosing-
Helps decide a safe starting dose for Phase I clinical trials.
Provides data on dose-response relationships and margins of safety.

Early Detection of Risks
Detects toxic effects early in development → prevents late-stage drug failures.

Saves time and money by eliminating unsafe compounds before clinical trials.
Supports Risk-Benefit Analysis
Provides data for regulators and clinicians to evaluate whether the benefits outweigh the risks.

Protects Public Health
Reduces chances of drug withdrawals from market due to hidden safety issues.
Maintains trust in medicines and pharmaceutical industry.

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Tier1 - CVS, CNS and respiratory safety pharmacology, HERG assay. Tier2- GI, renal and other studies

Safety pharmacology = studies that investigate undesirable pharmacodynamic effects of a drug on vital physiological functions. These are essential to support IND (Investigational New Drug) applications and ensure first-in-human safety.

Safety pharmacology is divided into Tier 1 (Core studies) and Tier 2 (Follow-up studies).

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Tier 1 (also called core safety pharmacology studies) are the mandatory tests required for all new drugs to check their effects on the most vital life-supporting systems:

Cardiovascular system (CVS)
Central Nervous System (CNS)
Respiratory system

-If a drug negatively affects these systems, it can cause serious harm or even death. That's why Tier 1 studies are always required before clinical trials.

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1. Cardiovascular System (CVS)-

Reason for testing:

Heart rhythm disturbances, blood pressure changes, or arrhythmias can be fatal.

Even small changes may lead to sudden cardiac death.

Parameters studied:

Blood pressure (↑ hypertension, ↓ hypotension)

Heart rate (bradycardia, tachycardia)

ECG (detects arrhythmias, QT prolongation)

Contractility (strength of heart pumping)

Models used:

Conscious telemetered dogs, monkeys, or rodents (measure BP, HR, ECG).

Isolated heart preparations (ex vivo).

hERG Assay (linked to CVS)-

Reason for testing:
Drugs may block the hERG (human Ether-à-go-go Related Gene) potassium channel in the heart.

This channel controls cardiac repolarization.
Blockade → QT interval prolongation → Torsade de Pointes (dangerous arrhythmia) → sudden death.

Test method:
In vitro assay using cells expressing hERG channels (usually patch clamp technique).
Checks whether the drug blocks these channels.

3. Central Nervous System (CNS)

Reason for testing:

CNS is sensitive → drugs may cause sedation, convulsions, hallucinations, or impaired motor activity.

Parameters studied:

General behavior (alertness, posture, grooming, aggression).

Locomotor activity (movement ↑ or ↓).

Motor coordination (rotarod test in rodents).

Reflexes (pupil response, startle reflex, pain response).

Body temperature (hypothermia, hyperthermia).

Seizure potential (pro-convulsant activity).

Models used:

Rodent functional observational battery (FOB).

Specific behavioral tests.

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3. Respiratory System-

Why important?

Many drugs depress breathing (e.g., opioids, anesthetics) → hypoxia and death.

Parameters studied:

Respiratory rate (breaths/minute)

Tidal volume (depth of breathing)

Minute volume (total air exchanged per minute)

Blood gases (O_2, CO_2 levels)

Methods used:

Plethysmography (whole-body plethysmograph in rodents).

Tracheal cannulation + direct airflow measurement in larger animals.

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Tier 2 (Supplementary / Follow-up Studies)-

Not always required → done when concern arises from Tier 1 studies, drug pharmacology, or adverse effects.

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1. Gastrointestinal (GI) System

Why important?

Drugs can alter motility, secretion → diarrhea, constipation, ulcer, nausea, vomiting.

Parameters studied:

GI motility (intestinal transit time, gastric emptying).

GI secretion (acid, pepsin, bile, pancreatic enzymes).

Emesis (nausea and vomiting).

Methods used:

Intestinal transit test (charcoal meal in rodents).

Gastric emptying test (marker dye or radioisotopes).

Fistula models in dogs (to measure secretion).

Ferret/dog emesis models (since rodents don't vomit).

2. Renal / Urinary System-

Why important?

Kidneys regulate fluid-electrolyte balance → drugs may cause nephrotoxicity, electrolyte imbalance, altered urine output.

Parameters studied:

Urine volume, osmolality, pH

Electrolyte excretion (Na^+, K^+, Cl^-)

Renal blood flow, GFR (glomerular filtration rate)

Plasma creatinine, BUN (markers of kidney function)

Methods used:

Renal clearance studies in animals.

Balance studies (intake vs excretion).

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3. Other Systems (Case-by-case)-

Autonomic Nervous System (BP reflexes, pupillary response).
Endocrine System (hormone levels, thyroid, adrenal).
Immune System (immune suppression, hypersensitivity).

Only performed if drug mechanism suggests possible risk.