CHAPTER-I

PHARMACOLOGICAL APPROACHES TO DRUG DISCOVERY

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General Principles

- Specific and general pharmacological studies should be conducted to support use of therapeutics in humans.
- In the early stages of drug development enough information may not be available to rationally select study design for safety assessment.
- In such a situation, a general approach to safety pharmacology studies can be applied.
- Safety pharmacology studies are studies that investigate potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range or above.
1. **Specific Pharmacological Actions**

- Specific pharmacological actions are those which demonstrate the therapeutic potential for humans.

- The specific studies that should be conducted and their design will be different based on the individual properties and intended uses of investigational drug.

- Scientifically validated methods should be used.

- The use of new technologies and methodologies in accordance with sound scientific principles should be preferred.

2. **General Pharmacological Actions**

3. **Essential Safety Pharmacology**
Safety pharmacology studies need to be conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range and above.

These studies should be designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; to evaluate adverse pharmacodynamic and/or pathophysiological effects observed in toxicology and/or clinical studies;

To investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected.
AIM OF ESSENTIAL SAFETY PHARMACOLOGY

- To study the effects of the test drug on vital functions. Vital organ systems such as cardiovascular, respiratory and central nervous systems should be studied.
- Essential safety pharmacology studies may be excluded or supplemented based on scientific rationale.
- Also, the exclusion of certain tests or explorations of certain organs, systems or functions should be scientifically justified.
Effects of the investigational drug should be studied on blood pressure, heart rate, and the electrocardiogram.

If possible in vitro, in vivo and/or ex vivo methods including electrophysiology should also be considered.
Central Nervous System

- Effects of the investigational drug should be studied on motor activity, behavioral changes, coordination, sensory and motor reflex responses and body temperature.
Respiratory System

- Effects of the investigational drug on respiratory rate and other functions such as tidal volume and hemoglobin oxygen saturation should be studied.
Follow-up and Supplemental Safety Pharmacology Studies

- In addition to the essential safety pharmacological studies, additional supplemental and follow-up safety pharmacology studies may need to be conducted as appropriate.

- These depend on the pharmacological properties or chemical class of the test substance, and the data generated from safety pharmacology studies, clinical trials, pharmacovigilance, experimental *in vitro* or *in vivo* studies, or from literature reports.
1) **Cardiovascular System**

- These include ventricular contractility, vascular resistance and the effects of chemical mediators, their agonists and antagonists on the cardiovascular system.

2) **Central Nervous System**

- These include behavioral studies, learning and memory, electrophysiology studies, neurochemistry and ligand binding studies.
3) **Respiratory System**
- These include airway resistance, compliance, pulmonary arterial pressure, blood gases and blood pH.

4) **Supplemental Safety Pharmacology Studies**
- These studies are required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety pharmacological studies and are a cause for concern.

5) **Urinary System**
- These include urine volume, specific gravity, osmolality, pH, proteins, cytology and blood urea nitrogen, creatinine and plasma proteins estimation.
6) Autonomic Nervous System

These include binding to receptors relevant for the autonomic nervous system, and functional response to agonist or antagonist responses in vivo or in vitro, and effects of direct stimulation of autonomic nerves and their effects on cardiovascular responses.

7) Gastrointestinal System

- These include studies on gastric secretion, gastric pH measurement, gastric mucosal examination, bile secretion, gastric emptying time in vivo and ileocaecal contraction in vitro.

8) Other Organ Systems

- Effects of the investigational drug on organ systems not investigated elsewhere should be assessed when there is a cause for concern. For example dependency potential, skeletal muscle, immune and endocrine functions may be investigated.
Conditions Under Which Safety Pharmacology Studies Are Not Necessary

- Safety pharmacology studies are usually not required for locally applied agents e.g. dermal or ocular, in cases when the pharmacology of the investigational drug is well known, and/or when systemic absorption from the site of application is low.

- Safety pharmacology testing is also not necessary, in the case of a new derivative having similar pharmacokinetics and pharmacodynamics.
Timing Of Safety Pharmacology Studies In Relation To Clinical Development

a) Prior To First Administration In Humans

- The effects of an investigational drug on the vital functions listed in the essential safety pharmacology should be studied prior to first administration in humans.

b) During Clinical Development

- Additional investigations may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development.
c) Before applying for marketing Approval

- Follow-up and supplemental safety pharmacology studies should be assessed prior to approval unless not required, in which case this should be justified.

- Available information from toxicology studies addressing safety pharmacology endpoints or information from clinical studies can replace such studies.

d) Application Of Good Laboratory Practices (GLP)

- The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.
THANK YOU