Pharmacological Approach To Drug Development

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Introduction

- **Pharmacology** is a scientific discipline that specialises in the mechanism of action, uses and undesired effects of drugs.

- Pharmacological studies should be conducted to support use of therapeutics in humans.

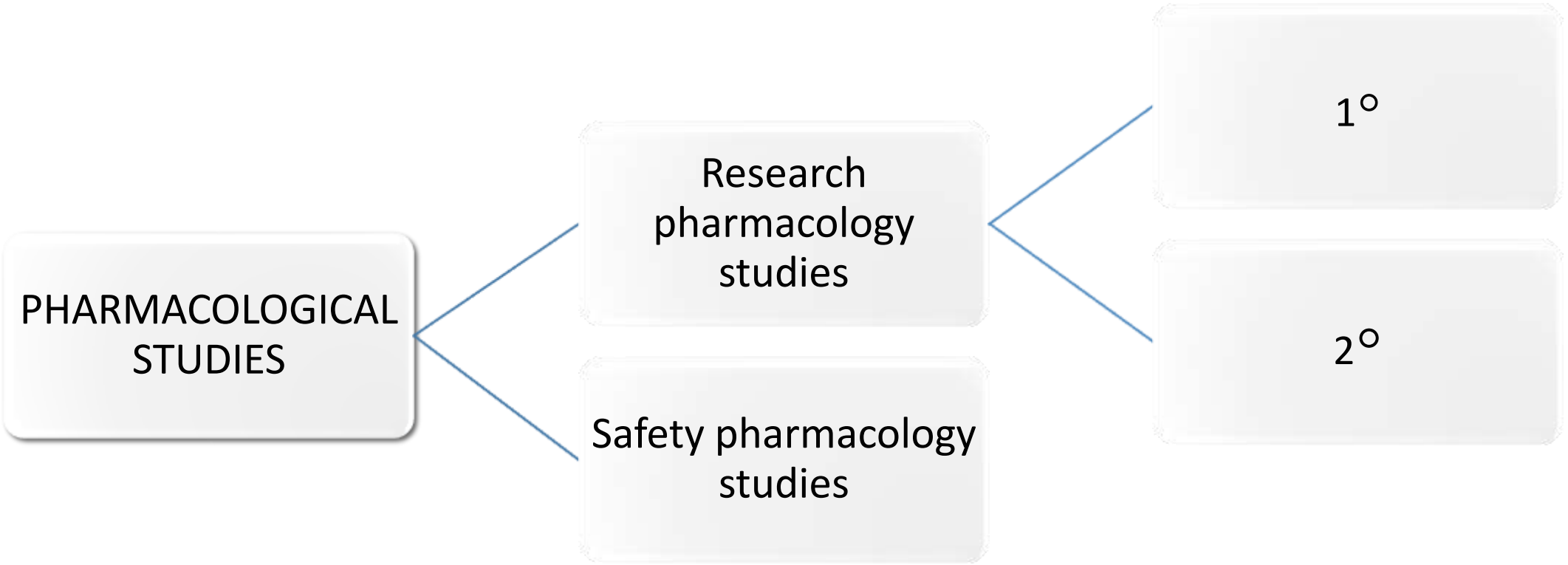
- In the early stages of drug development enough information may not be available to rationally select study design for safety assessment. In such a situation, a general approach to safety pharmacology studies can be applied.

- Animal pharmacology testing provides the initial conformation that the molecular targets is involved in a metabolic pathway or integrated physiological process that is abnormal in the disease state.

- Animal pharmacology studies allow the effects of the lead compound on the disease process (Pharmacodynamics) to be correlated with the concentration of compound need to achieve these effects (Pharmacokinetics).

- If the results of the tests suggest potential beneficial activity, related compounds are tested to see which version of the molecule produces the highest level of pharmacological activity and demonstrates the most therapeutic promise, with the smallest number of potentially harmful biological properties.

Types


PHARMACOLOGICAL STUDIES
Research pharmacology studies
Safety pharmacology studies
1°
2°

- Unlike primary and secondary pharmacology studies that explore the mode of action of the candidate drug and its effects related or unrelated to the therapeutic target, respectively, Safety Pharmacology identifies the “potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above”
- which are not identified by standard non-clinical toxicological studies.
- SP studies are, therefore, performed to ensure the safety of clinical participants in first in human (FiH) trials through improved decision-making in the selection of lead candidate drugs.

1. Research pharmacological studies:

➢Research pharmacological studies are conducted at the starting of a drug development program. They need to be performed to GLP standards.

➢ There are two types:

a) Primary research pharmacology studies

b) Secondary research pharmacology studies

a) Primary research pharmacology studies

- Primary actions are related to proposed therapeutic use.
- These studies focus on the mechanism of action of drug and can be conducted *in vitro* and *in vivo.*
- Studies conducted *in vitro* include radioligand binding studies and focus on drugs action on specific receptor sites
- Studies conducted *in vivo* investigate the pharmacological action of the drug in animal models.

b) Secondary research pharmacology studies

- Secondary actions focus on the overall pharmacological activity of the drug compound.
- And also relates to the actions that occur which is not directly related to the proposed therapeutic use.
- This can be conducted *in vitro* and *in vivo*. *In vitro* studies investigate the binding of the drug molecule with the non-target receptors.
- *In vivo* studies investigate the general pharmacological actions in animal models.

2. Safety pharmacology studies:

- 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.

- Safety pharmacology studies investigate potentially undesirable effects of the drug compound.

- They are conducted in animal models, that are single dose studies using intended therapeutic dose.

- *In vitro* studies should be designed to establish a concentration-effect relationship. The range of concentrations used should be selected to increase the likelihood of detecting an effect on the test system. The upper limit of this range may be influenced by physicochemical properties of the test substance and other assay specific factors.

- *In vivo* safety pharmacology studies should be designed to define the dose-response relationship of the adverse effect observed. When feasible, the time course (e.g. onset and duration of response) of the adverse effect should be investigated.

- The essential safety pharmacology is 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.

Examples

CVS	blood pressure, heart rate, and the electrocardiogram.
CNS	motor activity, behavioural changes, coordination, sensory and motor reflex responses and body temperature
RS	tidal volume and haemoglobin oxygen saturation should be studied.

Supplemental Safety Pharmacology Studies

- required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety pharmacological studies and are a cause for concern.

CVS	ventricular contractility, vascular resistance and the effects of chemical mediators, their agonists and antagonists on CVS
CNS	learning and memory, electrophysiology studies , neurochemistry and ligand binding studies.
RS	airway resistance, compliance, pulmonary arterial pressure, blood gases and blood pH.
Urinary system	urine volume, specific gravity, osmolality, pH, proteins, cytology and BUN, creatinine and plasma proteins estimation.
ANS	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
GIS	gastric secretion, gastric pH measurement, gastric mucosal examination, bile secretion, gastric emptying time *in vivo* and ileocaecal contraction *in vitro*.
Others	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.

Safety pharmacology studies are usually not required when;

- Product is to be used for local application, e.g. dermal or ocular
- The pharmacology of the investigational drug is well known
- Systemic absorption from the site of application is low
- Safety pharmacology testing is also not necessary, in case of a new derivative having similar pharmacokinetics and pharmacodynamics.
- For biotechnology-derived products that achieve highly specific receptor targeting.

Timing Of Safety Pharmacology Studies In Relation To Clinical Development

1. 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

2. During Clinical Development

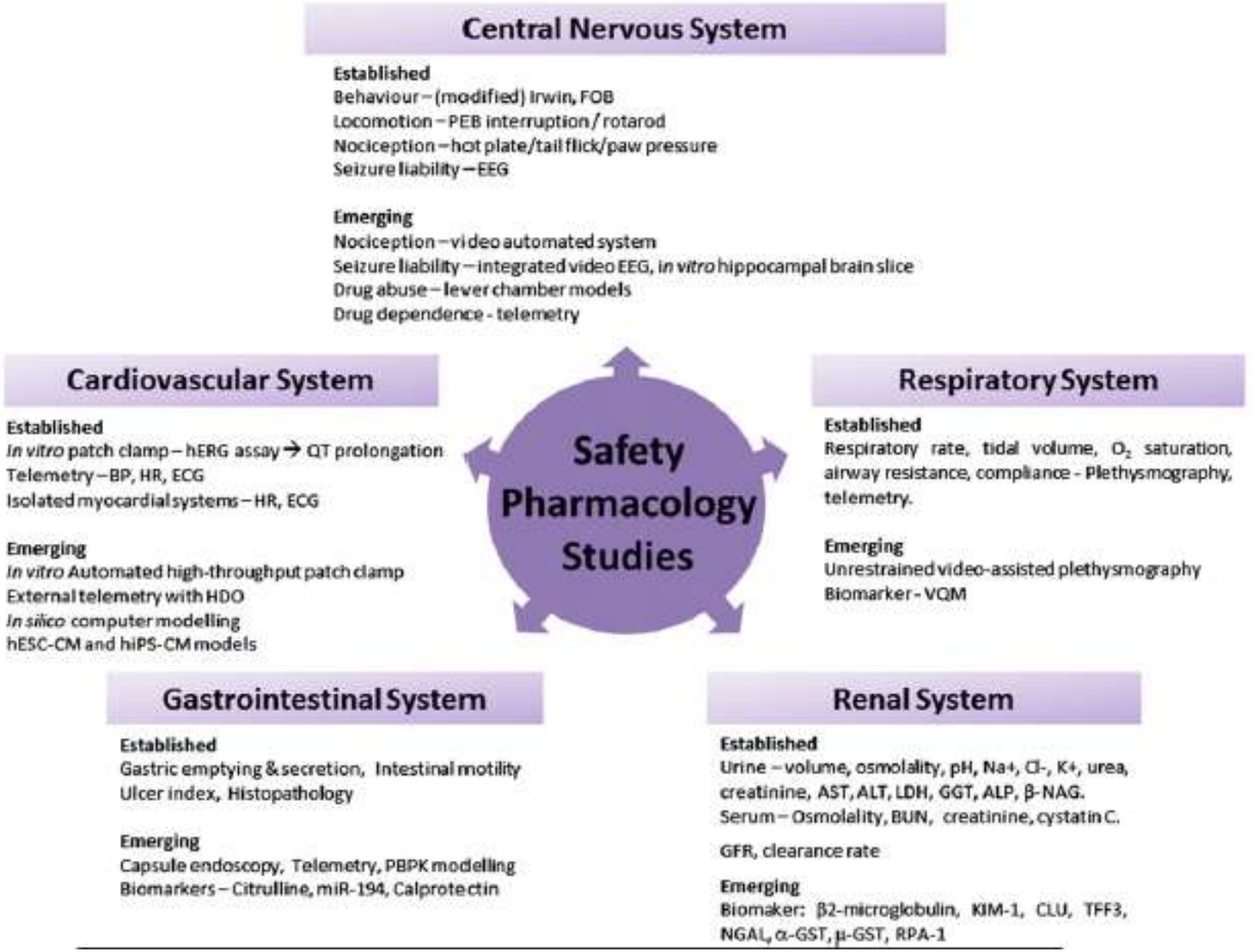
Additional investigations may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development

3. 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.

4. 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.


Central Nervous System
Established
Behaviour – (modified) Irwin, FOB
Locomotion – PEB interruption / rotarod
Nociception – hot plate/tail flick/paw pressure
Seizure liability – EEG
Emerging
Nociception – video automated system
Seizure liability – integrated video EEG, in vitro hippocampal brain slice
Drug abuse – lever chamber models
Drug dependence - telemetry
Cardiovascular System
Established
In vitro patch clamp – hERG assay → QT prolongation
Telemetry – BP, HR, ECG
Isolated myocardial systems – HR, ECG
Emerging
In vitro Automated high-throughput patch clamp
External telemetry with HDO
In silico computer modelling
hESC-CM and hiPS-CM models
Safety Pharmacology Studies
Respiratory System
Established
Respiratory rate, tidal volume, O2 saturation, airway resistance, compliance - Plethysmography, telemetry.
Emerging
Unrestrained video-assisted plethysmography
Biomarker - VQM
Gastrointestinal System
Established
Gastric emptying & secretion, Intestinal motility
Ulcer index, Histopathology
Emerging
Capsule endoscopy, Telemetry, PBPK modelling
Biomarkers – Citrulline, miR-194, Calprotectin
Renal System
Established
Urine – volume, osmolality, pH, Na+, Cl-, K+, urea, creatinine, AST, ALT, LDH, GGT, ALP, β-NAG.
Serum – Osmolality, BUN, creatinine, cystatin C.
GFR, clearance rate
Emerging
Biomaker: β2-microglobulin, KIM-1, CLU, TFF3, NGAL, α-GST, μ-GST, RPA-1

References

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THAN ‘Q’