ANIMAL EXPERIMENTS FOR DRUG DEVELOPMENT

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Stages of Drug development

- ❖ **Pharmacological Efficacy**
- ❖ **DMPK studies**
- ❖ **Safety Evaluation**

- ✓ **Animal use are essentially required**

PHARMACOLOGICAL EFFICACY

Animal models to demonstrate:
Specific Pharmacological action of a test substance and its therapeutic potential for humans.

Efficacy - **Effective dose (ED50) & comparison with standard drug (if possible)**
Probable mechanism (if possible)

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

- **Animal models are selected on the basis of validity**
- **Validity – usefulness of an animal model for a given purpose**
- **PREDICTIVE VALIDITY:**

Capability of a model to identify a property of test substance

ANIMAL MODELS USED AT CSIR-CDRI

- **CNS & CVS DISORDERS: Neurobehavioural Diseases, Stroke, Hypertension – Thrombosis, Atherosclerosis**

- **METABOLIC DISORDERS: Diabetes, Dyslipidemea, Osteoporosis**

- **Reproductive System: Fertility – Contraception**

- **Infectious Diseases: Malaria, Filaria, Leishmaniasis, Tuberculosis**

Screening programme:

- **In vitro to identify active molecule**
- **In vivo to establish efficacy**
- **ED 50 and comparative evaluation with standard drug to determine therapeutic potential**

Development phase:

Preclinical Drug Metabolism and Pharmacokinetics (DMPK) Studies of a candidate drug

- **DMPK is a major contributor to high rate of attrition, hence desirable DMPK is essential for clinical success of a candidate drug**

Analytical & Bionalytical Assay Methods

In-vitro Parameters:

- GI Stability
- In-situ Permeability
- Plasma Protein Binding
- In-vitro Metabolic Stability (Rat S-9 / Microsomal Study)
- CYP 450 Reaction Phenotyping
- Metabolite Profiling

In-vivo Parameters:

- Oral and i.v. pharmacokinetics
- Tissue distribution
- Metabolism
- Excretion studies (Feces, Urine, Bile)
- Toxicokinetics

BIOAVAILIBILITY, HALF-LIFE, ACTIVE METABOLITE & TISSUE ACCUMULATION are important for Human use

Safety Pharmacology Studies

- **Safety pharmacology studies are conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range and above.**

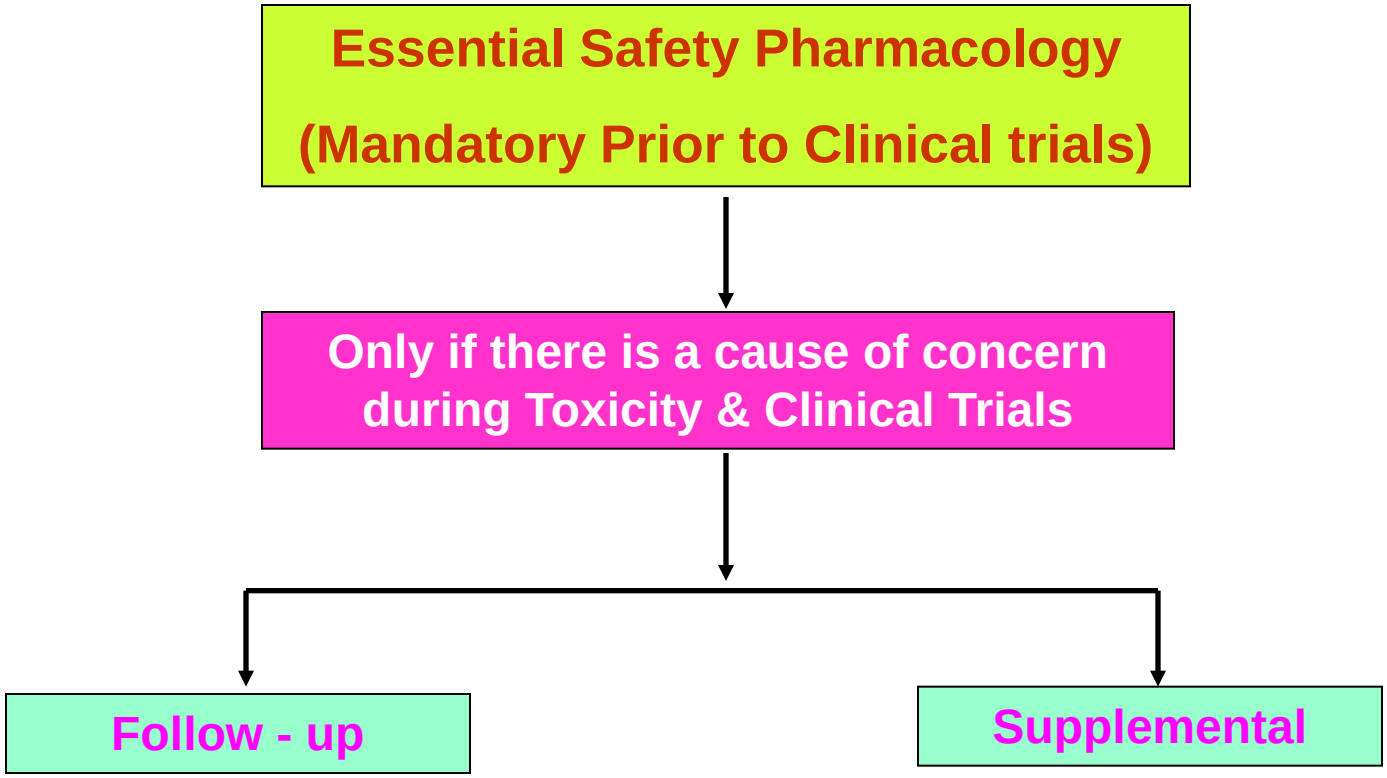
- These studies should be designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to

- ✓ **Human safety**;

- ✓ Evaluation of adverse pharmacodynamic and/or pathophysiological effects observed in toxicology and/or clinical studies; and

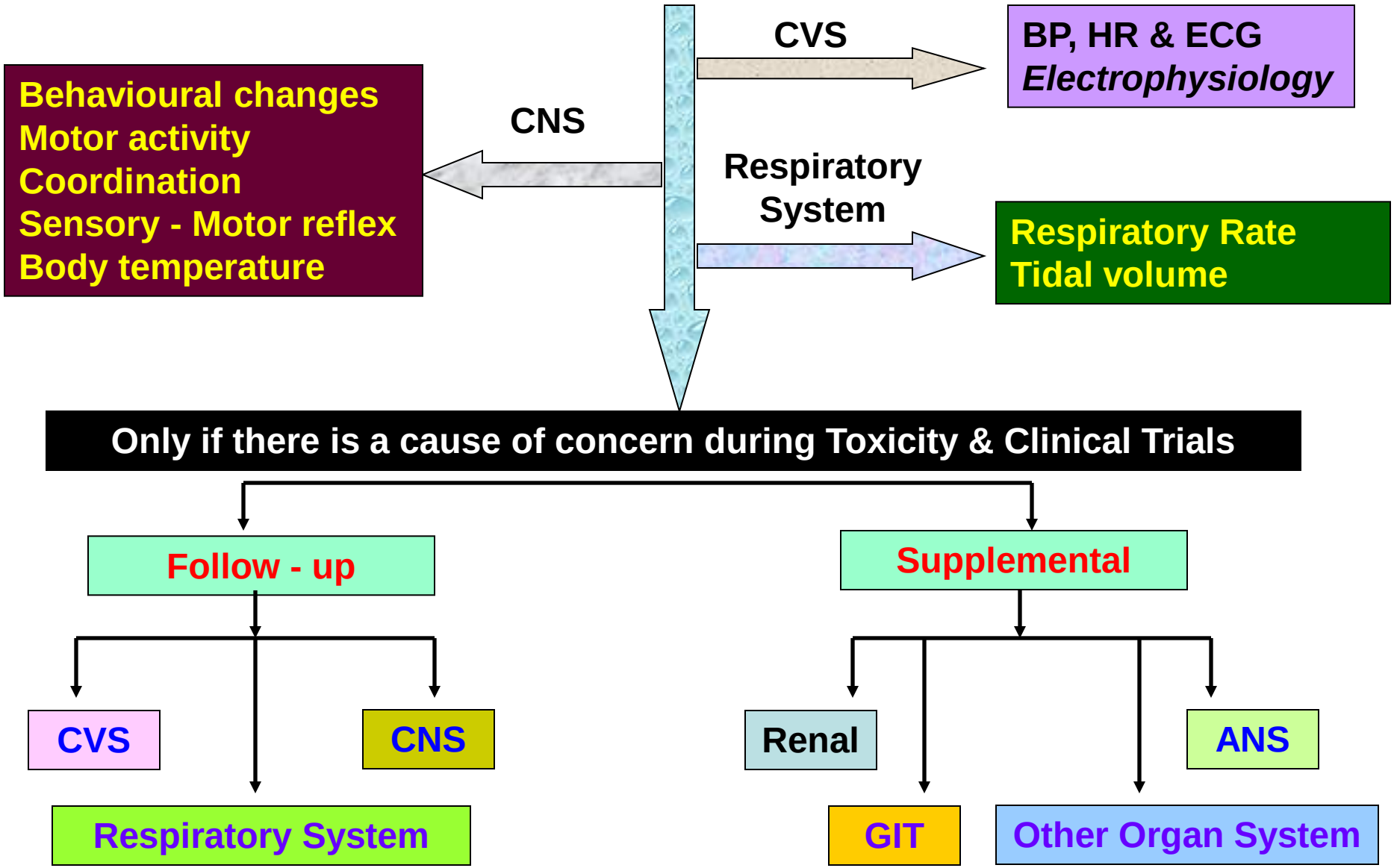
- ✓ Investigation of the mechanism of the adverse pharmacodynamic effects observed and/or suspected.

SAFETY PHARMACOLOGY STUDIES SCHEDULE Y-APPENDIX IV (Jan 2005)



Essential Safety Pharmacology

To assess the potential adverse effects of a candidate drug



Animal Toxicity Studies (Schedule Y Appendix III)

Objective: To Explore Toxic effects of a candidate drug

Systemic Toxicity Studies

Single Dose (Rodent)

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Dose ranging (DRF) (Rodent)

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Repeated Dose (Rodent & Non-rodents)

Parameters:

- General Behavior
- Organ Pathology: Gross & Microscopic
- Hematology
- Biochemistry (Blood)
- Urine analysis

Special Toxicity Studies

- **Reproductive Toxicity**
  (Male Fertility, Female Reproduction & Development: Fertility, Teratogenecity & perinatal)
- **Genotoxicity**
  (Gene mutation (Ames), Ch damage: Aberration Test & Micornucleus test)
- **Carcinogenicity**
- **Immunotoxicity**

Toxicity Studies Require to obtain permission for Phase I Clinical trial

Systemic Toxicity Study: Single , DRF & Repeated Dose

Duration of toxicity study	14 days	28 days	90 days	180 days
Duration in human	up to 1 week	>1 to 2 week	>2 to 4 week	>4 week
Speicies (n /sex/gp)	Rodent – Rat, (6-10) Non rodent- Rh Monkey / Dogs (2-3)	Rodent – Rat, (6-10) Non rodent- Rh Monkey / Dogs (2-3)	Rodent – Rat, (15-30) Non rodent- Rh Monkey / Dogs (4-6)	Rodent – Rat, (15-30) Non rodent- Rh Monkey / Dogs (4-6)

Special Toxicity Studies:

Reproductive Toxicity: Male Fertility Study

Genotoxicity: Ames test for mutation

FIRST HUMAN DOSE CALCULATION

Important Determinants

- ED 50 (Efficacy Pharmacology)
- NOAEL (Systemic Toxicology)

Thanks