

# Animal Experiments for Drug Development

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# Why do we need to discover a NEW DRUG?



- **Before 1950s it was common to hear people dying from various diseases due to lack of medicine.**
- **Now we have medicine for almost all diseases (although they may not be the best ones).**
- **People are protected against dangerous infections due to medical advances like vaccination and antibiotics**
- **New medicines for various systemic disorders save lives and reduce suffering for millions of people every day**
- **There is a need to develop better cures for various diseases in order to improve the quality of life of humans**

# Why Do We Need Animals in Drug Development



- Like human beings, mice rats, rabbits, dogs need to breathe air, pump blood around their bodies, and digest the food.
- So understanding how new medicine work in an animal provides valuable information about how it will help to treat human illness and predict most of the likely side effects
- Although scientists use a variety of *in vitro* cell based assays and enzyme based biochemical assays in our drug discovery process for screening of new molecules, animal experiments are unavoidable because *in vitro* assays do not adequately simulate the diseased condition.

# Cont,



- In order to establish the safety & efficacy of new drugs, various national & international (ICH) guidelines have been established, which involve use of animals.
- In India these have been specified in the “Schedule Y” of the Drugs & cosmetics Rules, 1945 and must be followed by everyone. Without these no permission can be given to anyone for testing any new molecules in humans.

# **Animal studies required before permission for human trials (Schedule Y Requirements)**



## **3. Animal Pharmacology**

### **3.1. Summary**

### **3.2. Specific pharmacological actions**

### **3.3. General pharmacological actions**

### **3.4. Follow-up and Supplemental Safety Pharmacology Studies**

### **3.5. Pharmacokinetics: absorption, distribution; metabolism; excretion**

## **4. Animal Toxicology**

### **4.1. General Aspects**

### **4.2. Systemic Toxicity Studies**

### **4.3. Male Fertility Study**

### **4.4. Female Reproduction and Developmental Toxicity Studies**

### **4.5. Local toxicity**

### **4.6. Allergenicity/Hypersensitivity**

### **4.7. Genotoxicity**

### **4.8. Carcinogenicity**



# Toxicology Studies



- Nonclinical toxicology studies are required to:
  - Estimate the safe starting dose for clinical studies
  - Assess toxic effects with respect to target organs; therefore, potential organ toxicities to be monitored in the clinical studies
  - Assess potential reversibility
  - Assess dose dependence
  - Assess relationship to exposure
  - Assess hazards like carcinogenicity , teratogenicity

## ➤ Systemic toxicity studies:

- Single-dose toxicity studies: in 2 rodent species (mice and rats) using same route as intended for humans
- Repeated dose systemic toxicity studies: In at least two mammalian species of which one should be a non-rodent

# Animal toxicology

- Male fertility study: One rodent species (preferably rat should be used)
- Female Reproduction & Developmental Toxicity studies:
  - Required for all drugs proposed to be studied or used in women of child bearing age
    - Female fertility study
    - Teratogenicity study
    - Perinatal study

# Animal toxicology

- Local toxicity – Required when new drug is proposed to be used by some special route (other than oral) in human e.g. skin, vaginal mucous membrane. If the drug is absorbed from the site of application appropriate systemic toxicity studies will also be required.
  - Dermal toxicity studies-for products meant to be used on skin
  - Ocular toxicity studies- for products meant for ocular instillation
  - Inhalation toxicity studies – using formulation to be eventually proposed to be used via inhalation.

Allergenicity / Hypersensitivity

Genotoxicity

# Animal toxicology

## Carcinogenicity

- If drug is expected to be clinically used for more than 6 month or used in an intermittent manner for chronic or recurrent conditions
- Studies required if carcinogenic potential is suspected in the same product class

# Animal toxicity requirement -Local toxicity studies

| Route of administration | Duration of human exposure | Human phase for which study is proposed | Tox requirement |
|-------------------------|----------------------------|---|-----------------|
| Dermal                  | Upto 2 wk                  | I, II                                   | 1 Sp; 4 wk      |
|                         |                            | III                                     | 2 sp; 4 wk      |
|                         | > 2 wk                     | I, II, III                              | 2sp; 12 wk      |
| Ocular or otic or nasal | Upto 2 wk                  | I, II                                   | 1 sp; 4 wk      |
|                         |                            | III                                     | 2 sp; 4 wk      |
|                         | >2 wk                      | I, II, III                              | 2 sp; 12 wk     |
| Vaginal or rectal       | Upto 2 wk                  | I, II                                   | 1 Sp; 4 wk      |
|                         |                            | III                                     | 2sp; 4 wk       |
|                         | >2 wk                      | I, II, III                              | 2 Sp; 12 wk     |

# Animal toxicity requirement-Systemic toxicity studies

| Route of administration                    | Proposed duration of use in human                     | Human phase for which study is proposed to be conducted | Toxicity requirement                       |
|--|---|---|--|
| Oral or parenteral or transdermal          | Single dose or multiple dose in one day, up to 1 week | I, II, III  | 2 sp; , 2 wk                               |
|  | >1 wk but upto 2 wk                                   | II, III   | 2 sp; , 4 wk                               |
|  | >2 wk but upto 4 wk                                   | II, III   | 2 sp; ,12 wk                               |
|  | Over 1 month  | II, III   | 2 sp; ,24 wk                               |
| Inhalation (general anaesthetics,aerosol ) | Upto 2 wk   | I,II,III  | 2sp;, 1 mt.<br>(exposure time 3h/d, 5d/wk) |
|  | Upto 4 wk   | II,III  | 2sp;12 wk (exposure time 6h/d, 5d/wk)      |
|  | >14 wk  | II,III  | 2sp; 24 wk<br>(exposure time 6h/d, 5d/wk)  |

# Toxicity Requirements for Phase I Clinical Trials

- Systemic Toxicity studies
  - (i) Single dose toxicity studies
  - (ii) Dose Ranging Studies
  - (iii) Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.
- Male fertility study
- In-vitro genotoxicity tests

# Toxicity Requirements for Phase I Clinical Trials (Contd...)

- Relevant local toxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure)
- Allergenicity / Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application)
- Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential)

# Toxicity Requirements for Phase II Clinical Trials

- Provide a summary of all the non-clinical safety data already submitted while obtaining the permissions for Phase I trial, with appropriate references.
- In case of an application for directly starting a Phase II trial - complete details of the nonclinical safety data needed for obtaining the permission for Phase I trial, as per the list provided above must be submitted.
- Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure
- In-vivo genotoxicity tests.
- Segment II reproductive/developmental toxicity study (if female patients of child bearing age are going to be involved)

# Toxicity Requirements for Phase III Clinical Trials

- Provide a summary of all the non-clinical safety data already submitted while obtaining the permissions for Phase I and II trials, with appropriate references.
- In case of an application for directly initiating a Phase III trial - complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and II trials, as per the list provided above must be provided.
- Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure

# Toxicity Requirements for Phase III Clinical Trials (Contd...)

- Reproductive/developmental toxicity studies
  - Segment I (if female patients of child bearing age are going to be involved), and Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development)
- Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).



**THANK YOU**