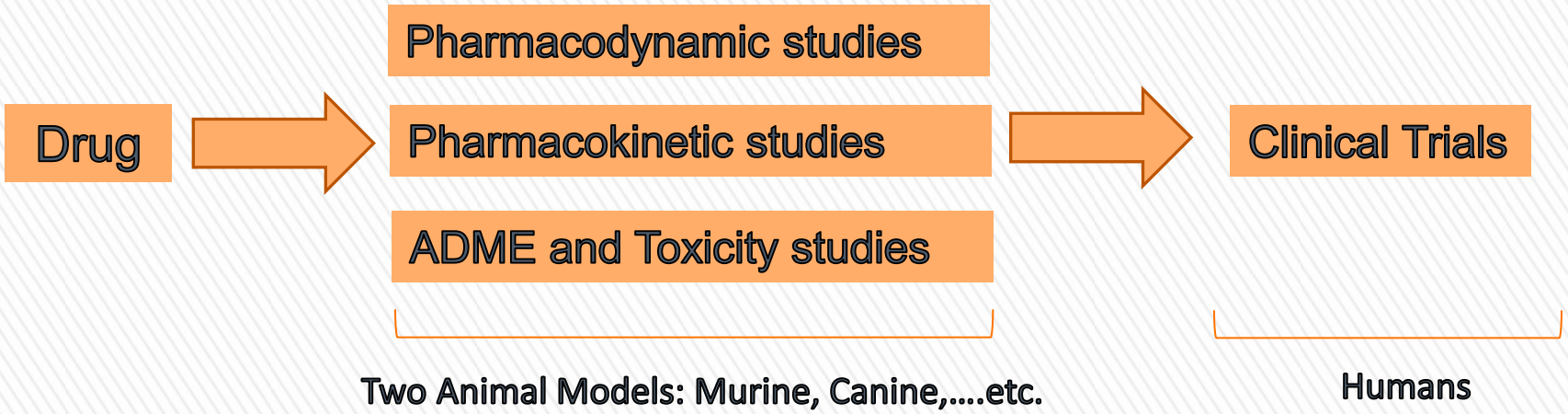
Laboratory of Pharmacology

- Pharmacological experiments are designed to study the effects of drugs on tissues, organs, and other living subjects
- Study the mechanism (s) by which the drug interact and affect the targets
- Qualitative Experiments: Study the Drug-Body interaction
- Quantitative Experiments: Study the amounts of active materials
- Clinical Trials: Study the effect (s)/side effect (s) of drugs on humans

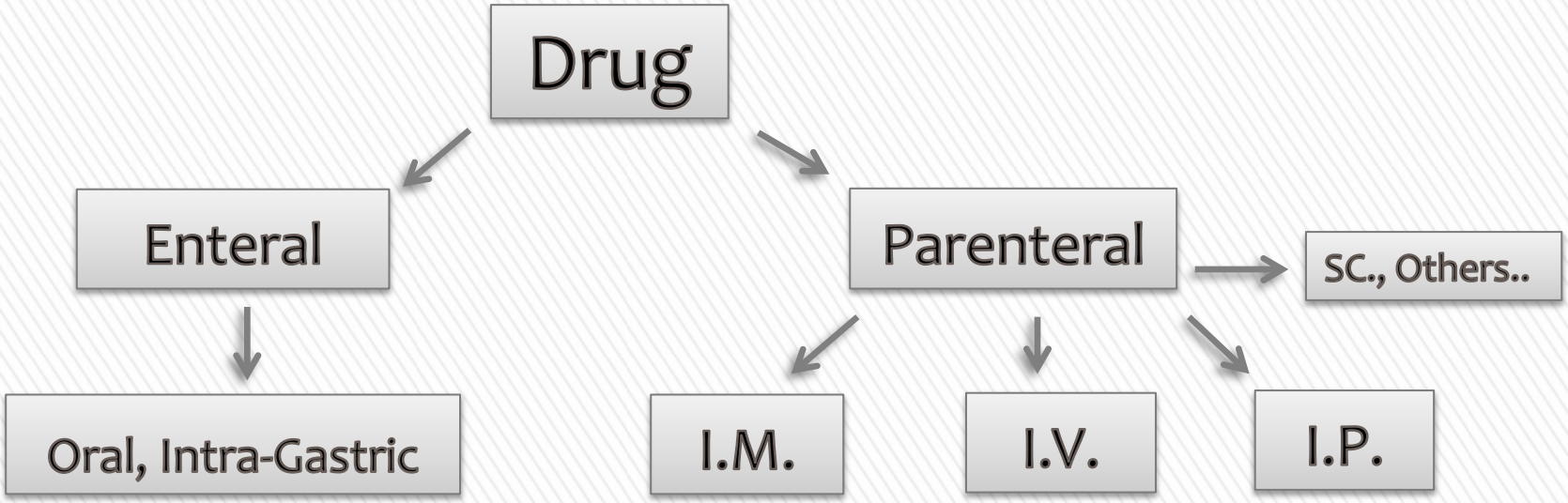
Significance of Pharmacological studies

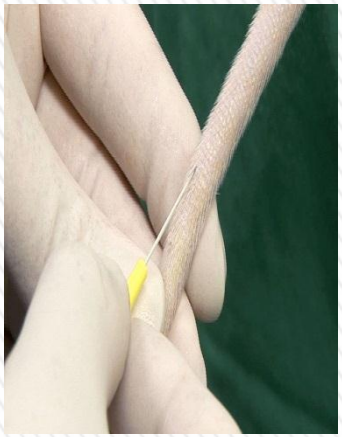
- **Drug Development:**



- **Evaluating and Exploring doses, mechanisms, side effects,… etc.**

Routes of Drug Administration





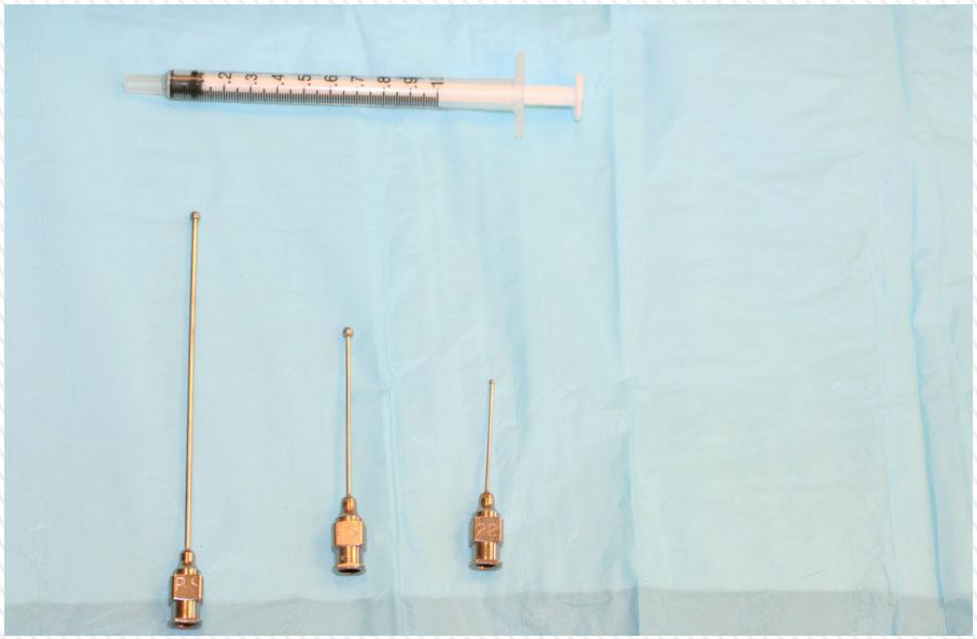
Routes of Drug Administration

- **Factors that should be considered before the administrating any substance (therapeutic or experimental) to an animal subject:**
  - pH
  - Sterility
  - Chemical nature (odor, taste, mucosal irritability, osmolarity, solubility, light sensitivity, and hazard status)
  - The dose to be administered, frequency of administration, volume to be administered, and the solvent (if necessary)
  - Route of administration
- **The route of administration is determined primarily by :**
  - The properties of the drug (ex. water or lipid solubility, ionization,…)
  - Therapeutic objectives (ex. the need for a rapid onset of action, the need for long term administration , restriction to a local site,…)

Routes of Drug Administration

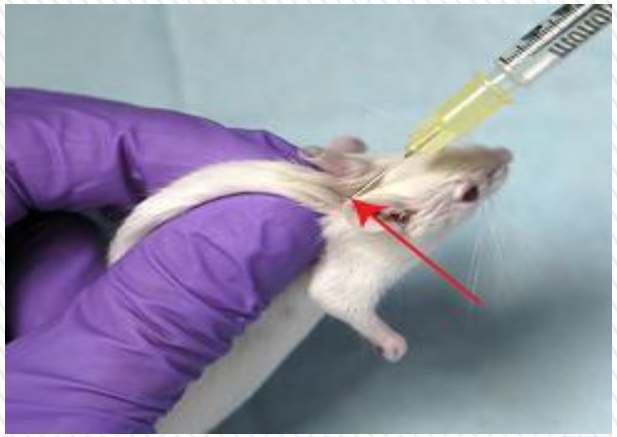
- Enteral Route of administration
  - **Additives to the drinking water:** The investigator must monitor the animal(s) and assure that adequate fluid intake occurs
  - **Additives to the food:** The investigator must monitor the animal(s) and assure that adequate food intake occurs
  - **Intra-gastric via gavage:**
    - Oral, or gastric, gavage is the administration of fluids directly into the lower esophageal or stomach using a ball ended feeding needle introduced into the mouth and thread down to esophagus
    - Gavage (esophageal or gastric) is often used in research settings, instead of mixing substances in water or food, to ensure accurate dosing of animals
    - The investigator must be trained and well experienced with gavage

Enteral Route



Routes of Drug Administration

- Parenteral routes of administration
  - The choice of parenteral route of administration will depend on the volume and material to be injected, and the desired rate of absorption
- **Subcutaneous (SC) injections**
  - The best spot to inject Subcutaneously is the loose skin on the back of the neck
  - A mouse may easily be injected by one person, whereas a rat may require restraint by one person and injection by the other
  - Not suitable for large volumes. Suitable for some insoluble suspensions



Routes of Drug Administration

- **Intraperitoneal (IP) injections**
  - Commonly used in rats and mice since muscle mass is so small and veins are difficult to find
  - Rapid absorption (almost as fast as IV) due to large peritoneal surface
  - IP administration results in a faster absorption into the vasculature than SC administration
  - Suitable for irritating compound, such as ketamine or pentobarbital
  - A mouse may easily be injected by one person, whereas a rat might require restraint by one person and injection by the other.

Intraperitoneal (IP) injections

- The injection site is usually on the animal's right lower abdominal quadrant
- Insert the needle at approximately 45 degree angle

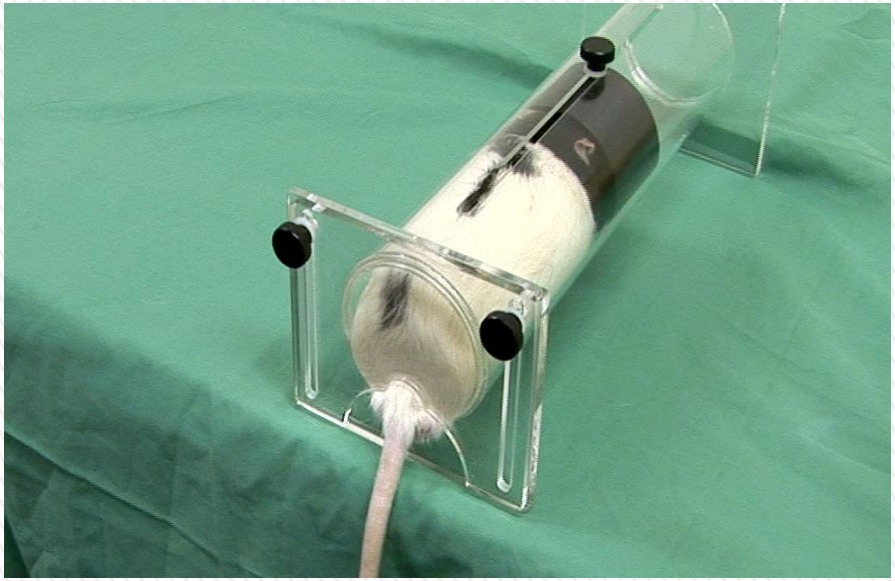
Routes of Drug Administration

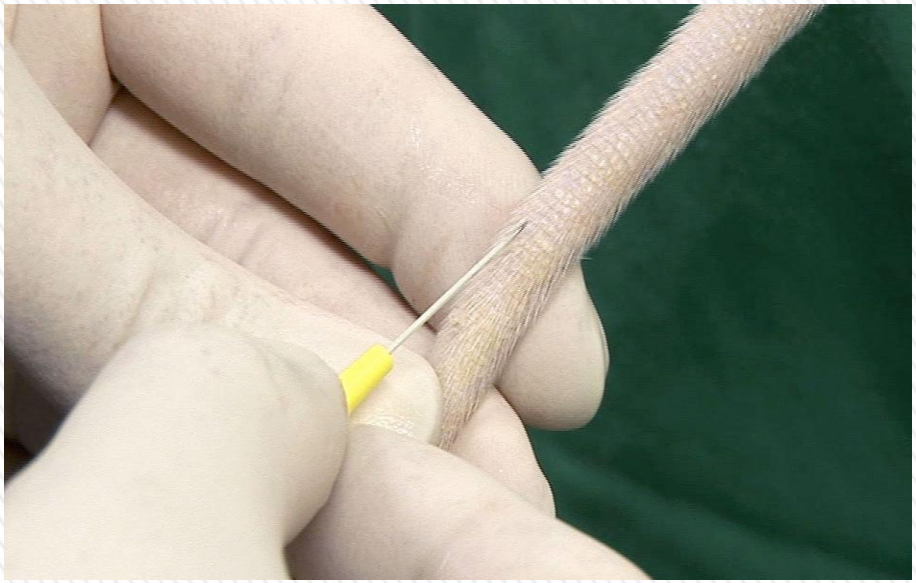
Intraperitoneal (IP) injections

- Complications of IP
  - The potential for serious side effects such as peritonitis
  - The risk of injecting the GI tract, kidneys, loop of bowel, and bladder (may also cause its rupture or other vessels in the area)
  - Some substances may cause mild-moderate irritation

Routes of Drug Administration

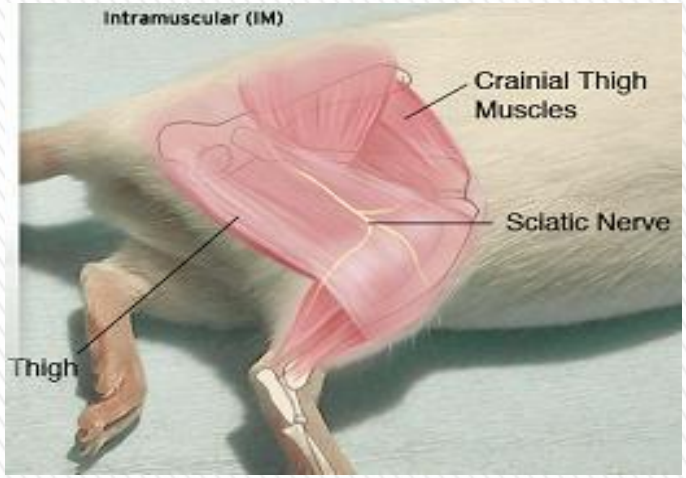
- **Intravenous (IV) injections**
  - Also called Tail vein injections, is one of the commonly used route
  - Technically difficult, and the use of a restraining device with appropriate size for the animal to be injected, is often required
  - Performed in mice and rats, use the lateral tail vein located on either side of the tail
  - Suitable for large volumes. Must inject slowly. Not suitable for oily solutions or insoluble substances.

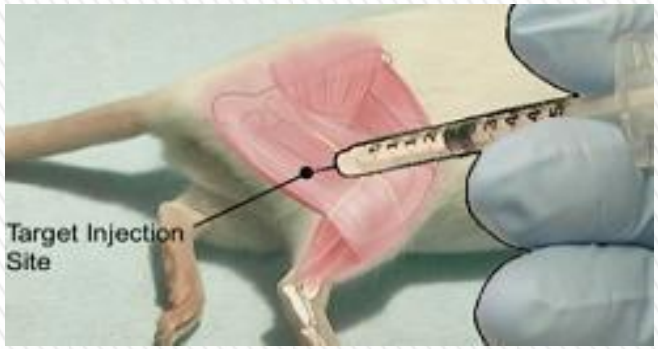




Routes of Drug Administration

- **Intramuscular (IM) injections**
  - Not recommended in mice due to their small muscle mass
  - In rats, ≤ 0.2 ml/site may be injected into gluteal muscles
  - Suitable for some moderate volumes, oily vehicles, and some mildly irritating substances





Characteristics Of Drugs And Solvent (Vehicle)

- **pH of the compound**
  - Knowing the pH of the compound and the vehicle is crucial for the administration of the drug
  - Aim for pH around 7, if the pH is higher or lower then
    - Buffer to pH 7 if possible
    - Dilute the solution using sterile normal saline
  - Injecting a high or low pH preparation as IM or SC would be painful and cause tissue necrosis
  - Examples:
    - Pentobarbital is a very basic pH (~11). It Can only be administered as IV or IP injections
    - Ketamine has an acidic pH (~4). It is administered as IP. IM administration can cause tissue necrosis

Characteristics Of Drugs And Solvent (Vehicle)

- **Taste and Odor**
  - Drugs having bitter tastes cause low subject compliance
  - Many taste-masking techniques, such as physical barrier coatings, chemical modification and sensory masking
  - Ex. tetracycline, doxycycline and metronidazole
  - Adding 2.0-5.0 g sucrose/100 ml water making the solution 2-5% sucrose enhances palatability
- **Mucosal irritability**
  - Check tissue compatibility when administering any compounds to mucosal surfaces, i.e. eyes, mouth and trachea

Characteristics Of Drugs And Solvent (Vehicle)

- **Solubility**
  - Insoluble compounds may require to be administered as a suspension
  - Example is sulfamethoxazole-trimethoprim which administered as a suspension in the drinking water. This suspension must be shaken daily to assure proper dosage
- **Light sensitivity**
  - Protect against light exposure either by dispensing in a colored glass or cover clear glass or plastic with foil

Characteristics Of Drugs And Solvent (Vehicle)

- **Solvents (vehicle) characteristics**
  - Wide range of vehicle types are available, ex.:
    - **Water:** For enteral administration only.
    - **Corn oil:** Gavage administration only.
    - **Sesame oil:** Gavage administration only.
    - **Ethanol: ?**

Laboratory Animals

Rats were first used for experimental purposes in the mid 1800s

Carefully bred rats are used in animal testing for a number of reasons, including their frequent reproduction, genetic purity and similarities to human biology

Lifespan	2.5-3.5 years
Adult weight	M 300-500g, F 250-300g
Birth weight	5-6g
Heart rate	330-480 beats/minute
Respiratory rate	85 breaths/minute
Body temp.	35.9-37.5°C

Rats

Rats are generally fed a diet containing low fiber, protein and fat

Rat rooms are usually maintained at 30-70% relative humidity and a temperature of 18-26°C

Rats should be acclimatized to handling to reduce stress

Blood can be collected from several sites in the rat including tail vein, retro-orbital sinus, vena cava or cardiac puncture

Can receive oral, IP, IM, and IV

Laboratory Animals

Mice

Lifespan	1-3 years
Adult weight	M 20-30 g, F 18-35g
Birth weight	1-2 g
Heart rate	310-840 beats/minute
Respiratory rate	80-230 breaths/minute
Body temp.	36.5-38°C

The mouse and human genomes are about 85 percent the same, and those similarities have made the mouse a powerful model for studying human biology and disease

Easy to make disease models

Handling, blood collection, and drug administration: same as rats