# Role of QAU in Toxicology with Special Reference to Inhalation Toxicology*

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# This presentation is based on following References/guidelines

- **Timothy Mcgovern, SciLucent, LLC, Herndon, Virginia, US.**
- **Alexander inhalation toxicol, et. al(2008)**
- **Considerations for toxicology studies of Respiratory Drug Products-regulatory Toxicol and Pharmacol. 25, 189., 1997**
- **ICH guidance M3 - R2**
- **US FDA May 2006-guidance document for pediatric drug development**

# Inhalation Toxicology: FDA's Expectations

- Generation and Characterization of Aerosols in Inhalation Chamber
- Drug Delivery to Target Organ (Lungs)
- Calculation of Delivered Dose
- Carcinogenicity in two rodent species
- Repro-tox and Genotox studies
- Juvenile toxicity

# Inhalation Toxicology: FDA's Expectations

- Conduct according to GLP and QA audits
- Route/s of exposure e.g. in Reprotox & carci studies
- Clearly described protocols with adequate duration to support clinical trials (ICH – M3 - R2)
- Basis and justification of dose selection
- Particle size and quantum of dose
- Species rodent (rat) and non-rodent (dog)

# Inhalation Toxicology: FDA's Expectations

- FDA publications does not address:

  Pulmonary dose calculation in animal studies

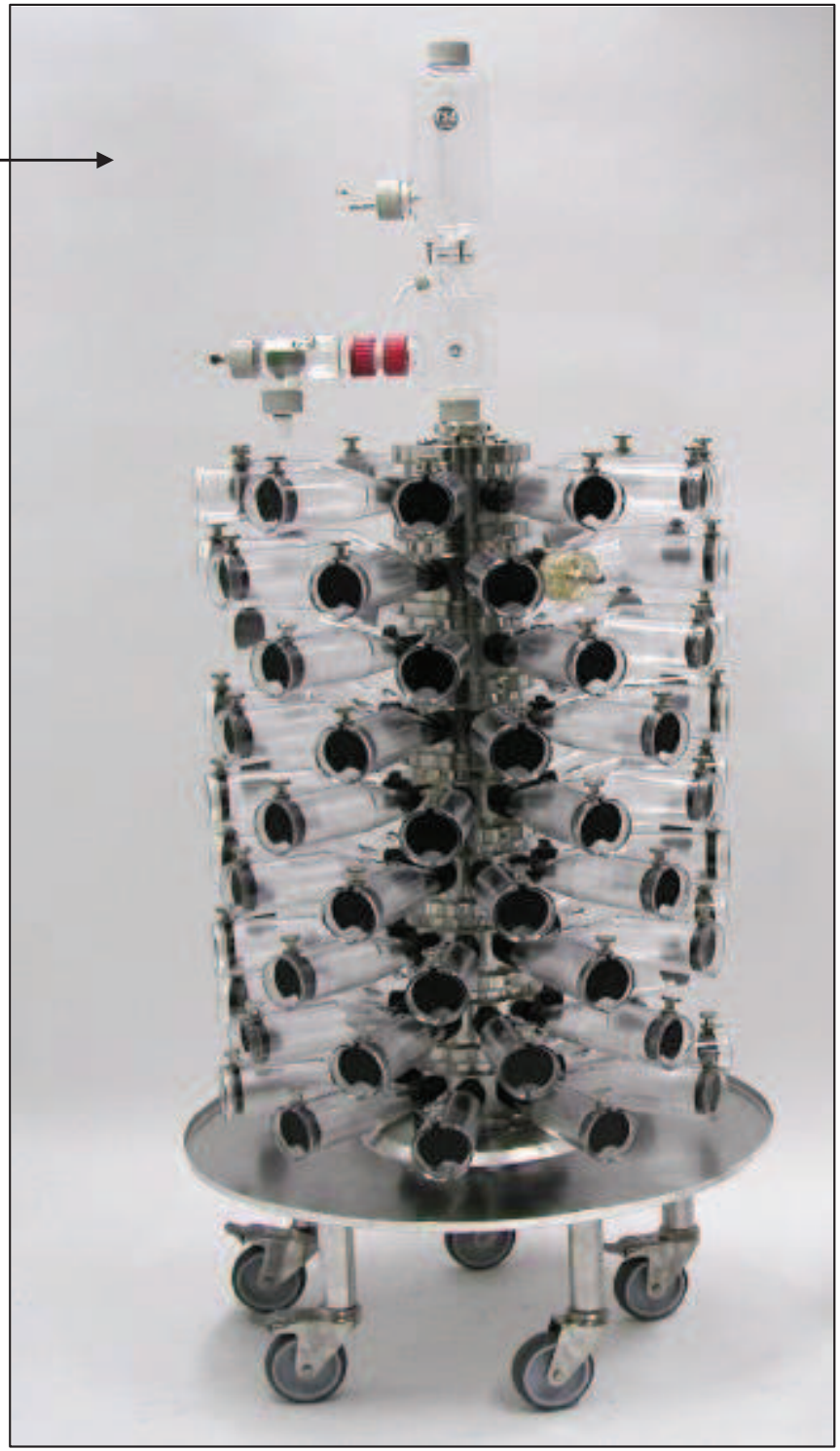
  Extrapolation to clinical doses based on the calculated deposited dose

This is especially important since 'Goal' is often to avoid significant systemic exposure
(e.g.: corticosteroids)

# Inhalation Toxicology: FDA's Expectations

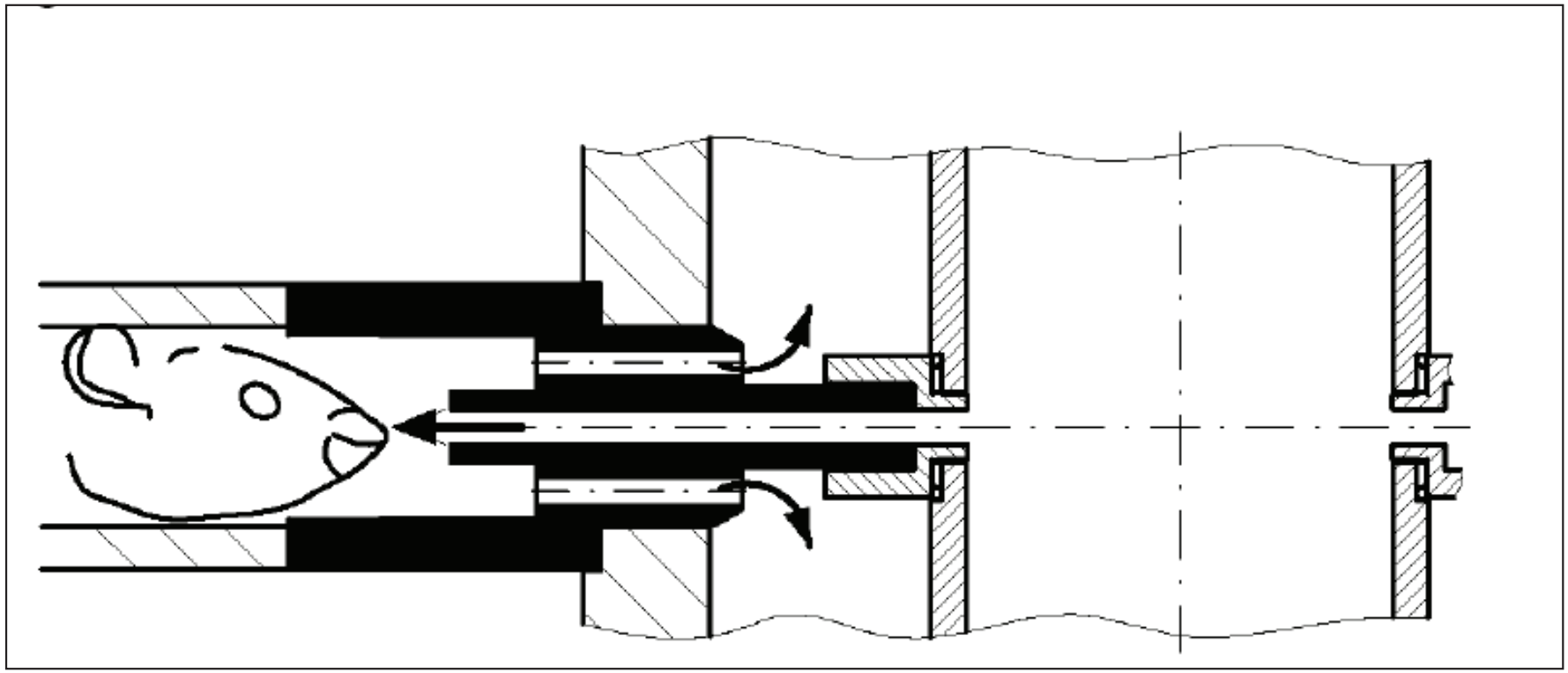
- Study design may require 2 controls i.e. sham/air and vehicle (if new/novel)
- Modes of exposure:
  - Rodents : Nose-only
  - Non rodents : Face-mask
  - Juvenile tox : Cone/whole-body
- ADME and TK
- Initial clinical dose: 1/10 or 1/6 the NOAEL respectively of rat and dog

**Rat: Inhalation Systems**



# Rat Inhalation nose-only unit with rats in place

# Aerodynamics of Inhalation unit



**Dog: Inhalation Systems**

# Complicated dose-Calculation in IH Toxicity

- **Dosing is usually a theoretical estimate and the doses vary with following variables:**

  **Mode of exposure( Nose only Vs Oral inhalation)**

  **Particle size (MMAD)***

  **Anatomic location (e.g. Pulmonary, Extra thoracic or Intranasal)**

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***MMAD is defined as the diameter at which 50% of the particles by mass are larger and 50% are smaller**

# Exposure Calculation of inhalation toxicity studies

$$DD = \frac{C \times RMV \times D(\times IF)}{BW}$$

DD = delivered dose (mg/Kg); C = concentration of substance in air (mg/L); RMV = respiratory minute volume or the volume of air inhaled in one minute (L/min); D = duration of exposure (min); IF = proportion by weight of particles that are inhalable by the test species, the inhalable fraction (IF ≈ 1 provided that the aerosol has reasonable respirability for the intended species); BW = bodyweight (Kg).

RMV for mice, rats, dogs and NHP should be calculated according to the formula:

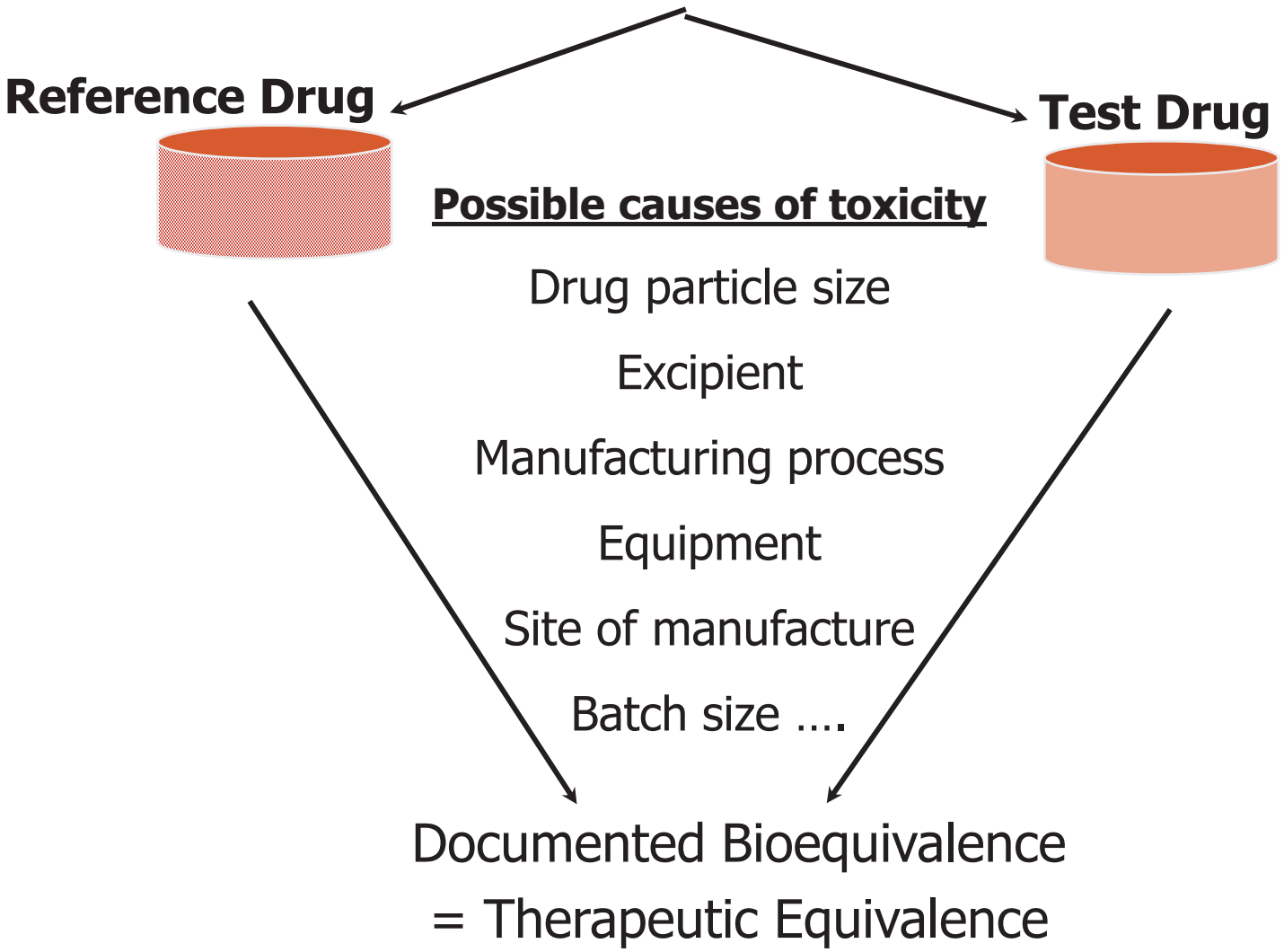
$$RMV(L/min) = 0.608 \times BW(Kg)^{0.852}$$

Based on *Association of Inhalation Toxicologists (AIT) Working Party Recommendation (2008)*

# Initial Clinical Dose

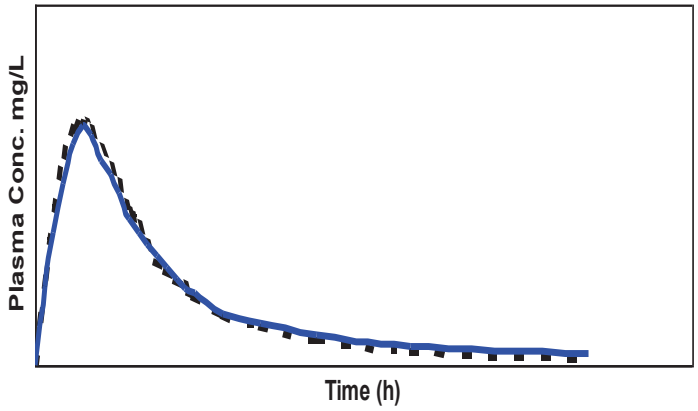
- **Initial clinical dose is usually <1/10 NOAEL in rats and < 1/6 in dogs on a mg/kg BW basis**
- **Doses may be selected on body surface area**
- **Narrow safety indices are acceptable**
- **PK/TK information is useful for if human PK/TK data available**

# Inhalation Toxicology of New Formulations

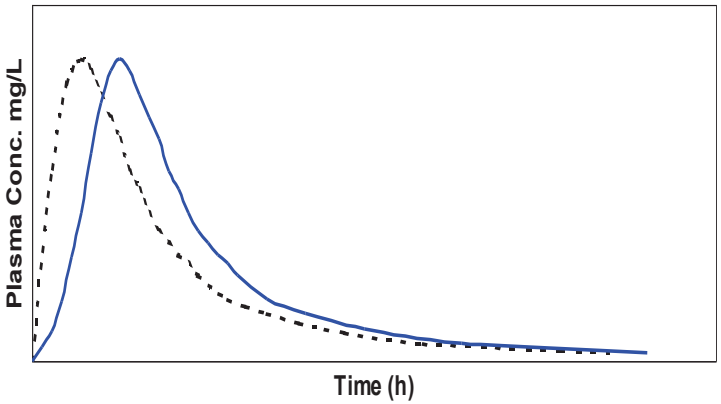


# Toxicokinetics **Food effect:**

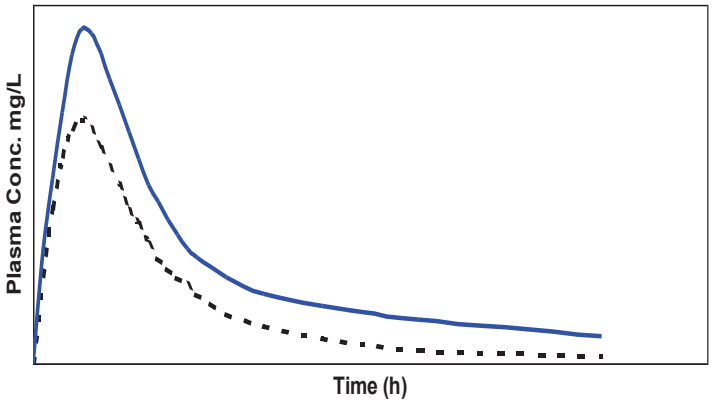
## No change in absorption



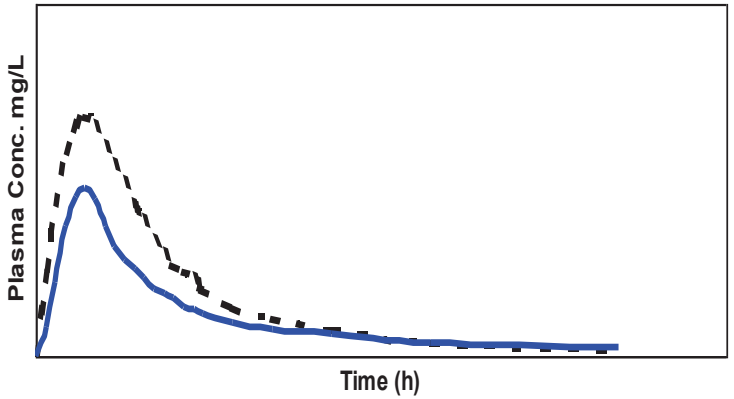

## Delay in absorption:



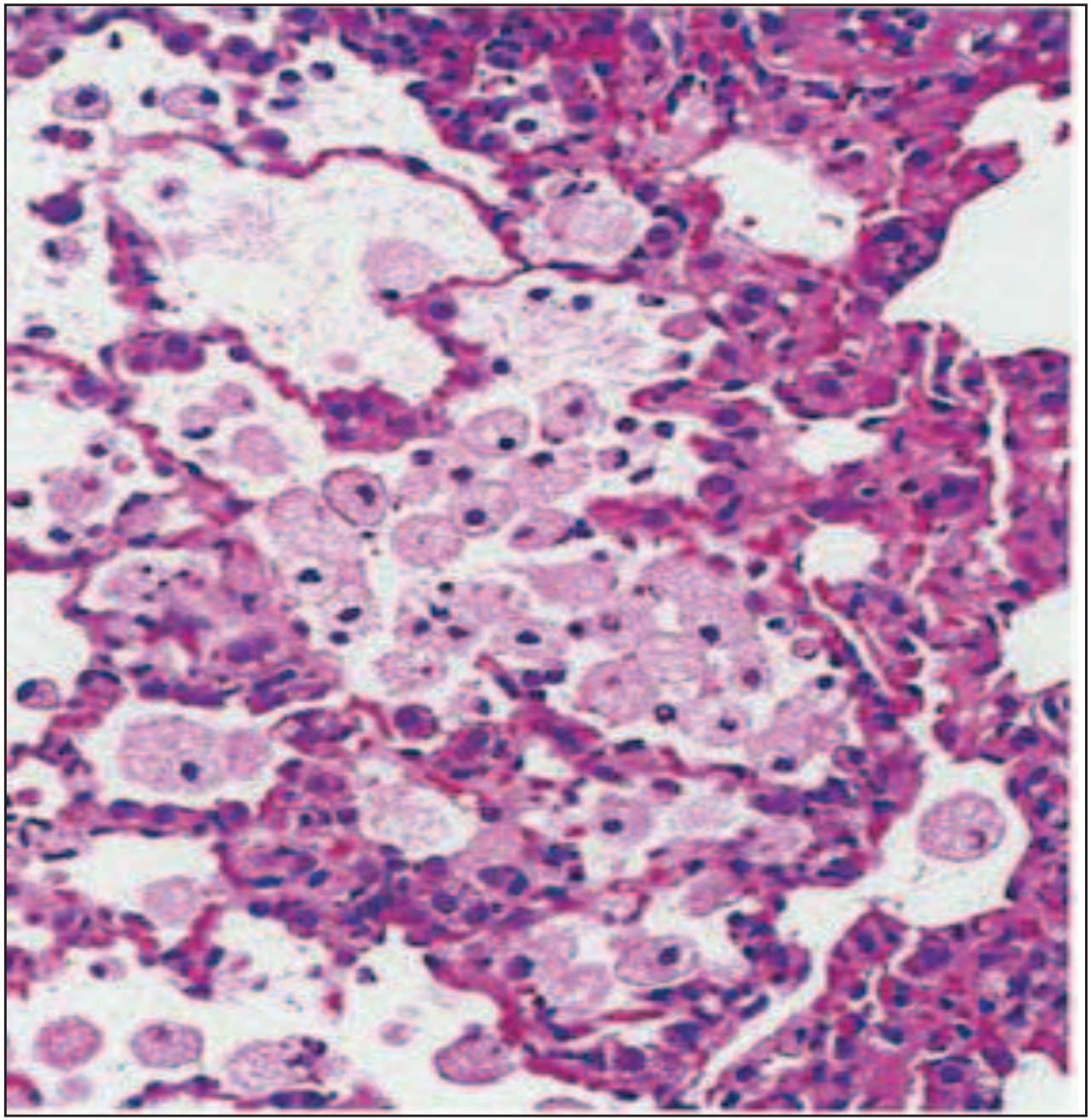

## Increase in absorption:




## Decrease in absorption:

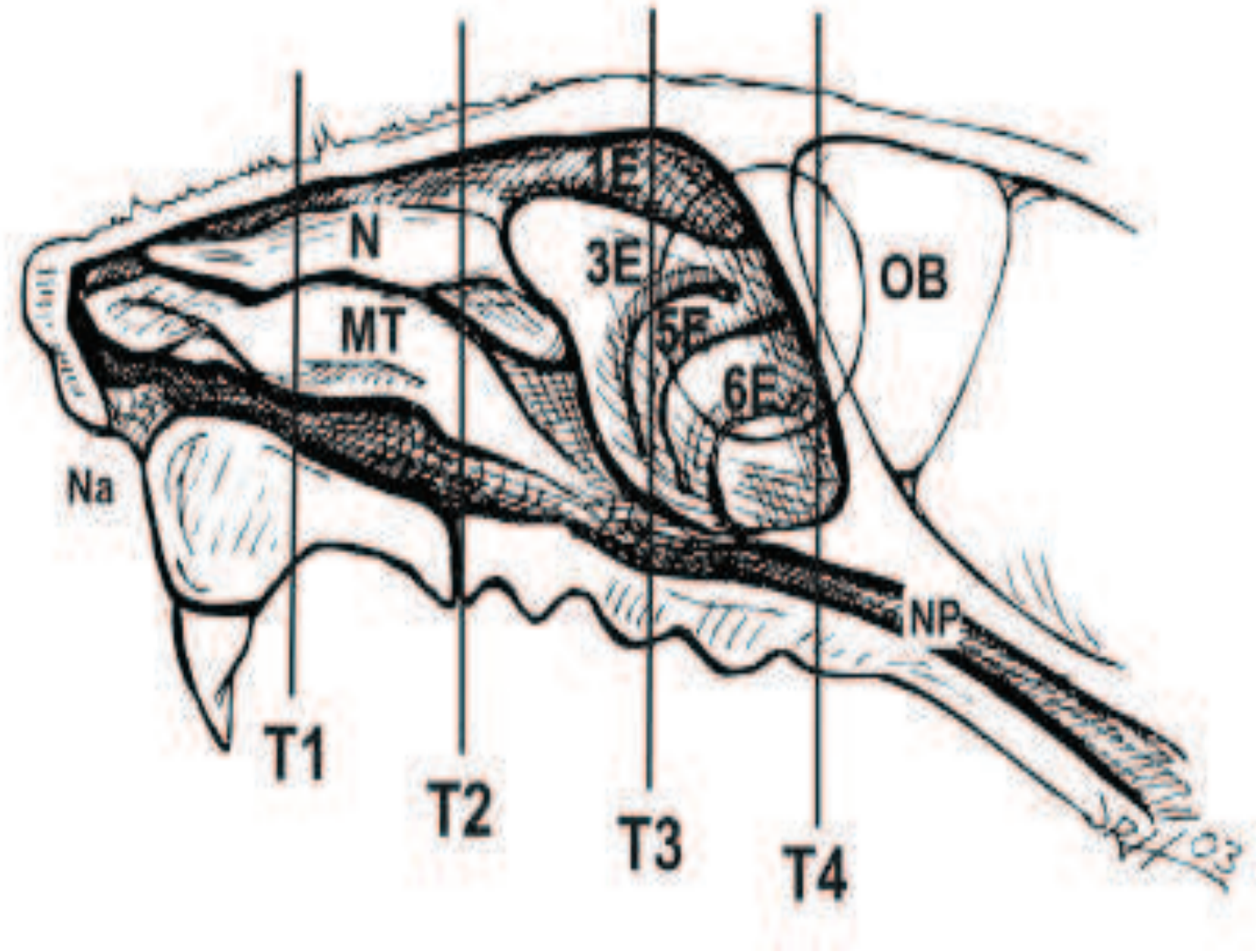


# Lung - Alveolar Histiocytosis



**100X**

# Recommended Site for Sections at Nasal Cavity



# Juvenile Inhalation toxicity

# Age Classification of Pediatric Patients

| | |
|---|---|
| Preterm newborn infants | Born prior to 38 weeks of gestation |
| Term newborn infants | 0 to 27 days of age |
| Infants and toddlers | 28 days to 23 months of age |
| Children | 2 to 11 years of age |
| Adolescents | 12 to 16-18 years of age |

*Source:* Modified from *Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (2000).

# Juvenile Toxicity Study Designs

- There is no STANDARD study design. It is dynamic on case by case basis
- Stage and different pace of organ system development in animal should correlate those in humans.
- The conduct of a preliminary (dose range-finding) study is highly recommended.

- **Start GLP study *only* after regulatory approval**

# Juvenile Toxicity Study Designs

- SPECIES: generally one species, rodent (rat) the preferred choice. Non-rodent species (rabbit, dog, NHP) may be required if scientifically justified.

  - Rats and mice are well characterized with regard to growth and development, large number of historical data on reproductive, developmental and general toxicity.

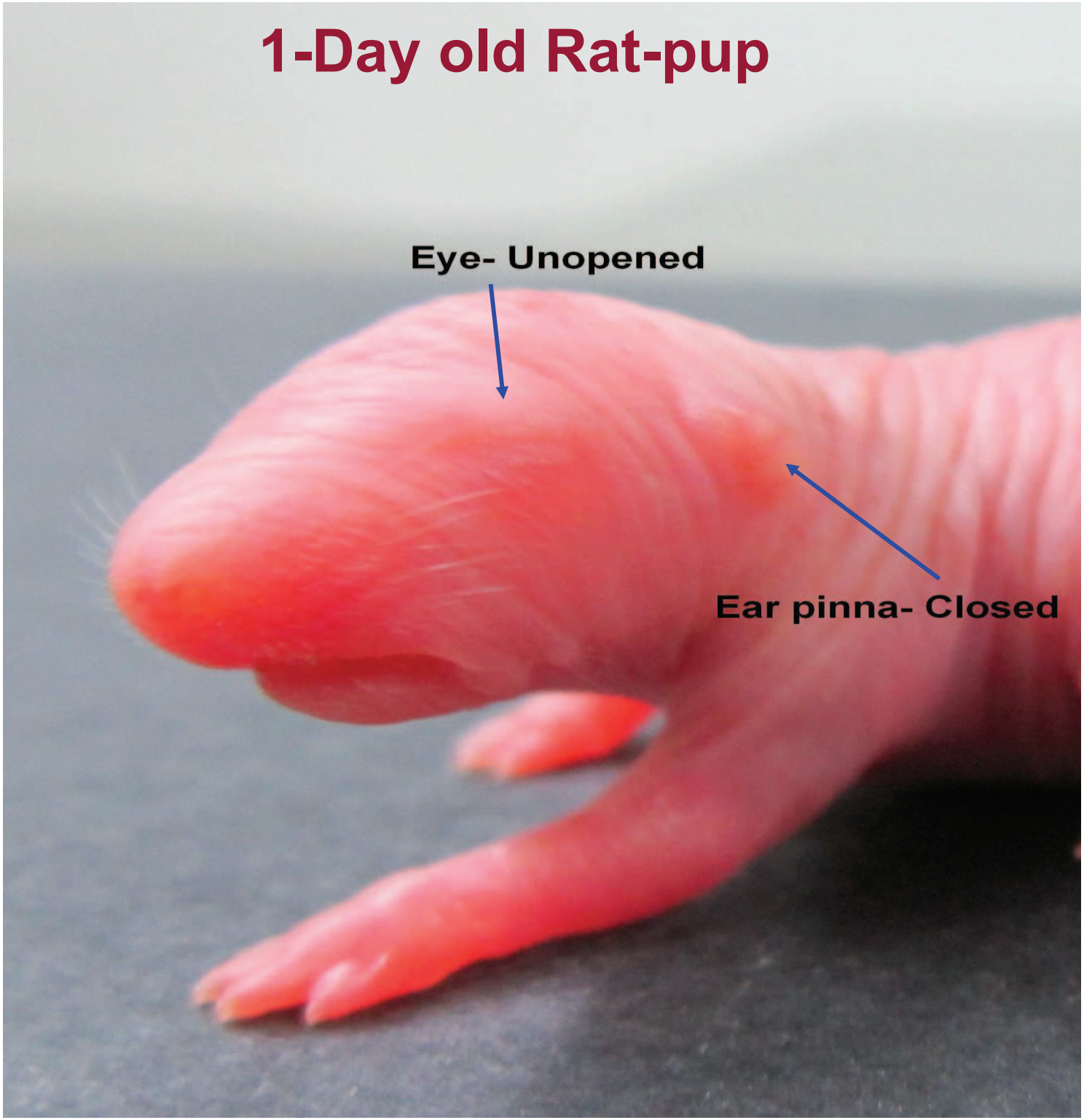
# Juvenile Inhalation Toxicity Study

## Special consideration: technical feasibility

## Earliest Starting Day for Inhalation Route

| Inhalation route | Rat | Mouse | Rabbit | Dog |
|---|---|---|---|---|
| Whole body (chamber) | PND 4 | PND 4 | PND 6 | PND 10 |
| Nose/mouth only (cone, mask) | PND 21 | PND 21 | PND 28 | PND 4 |

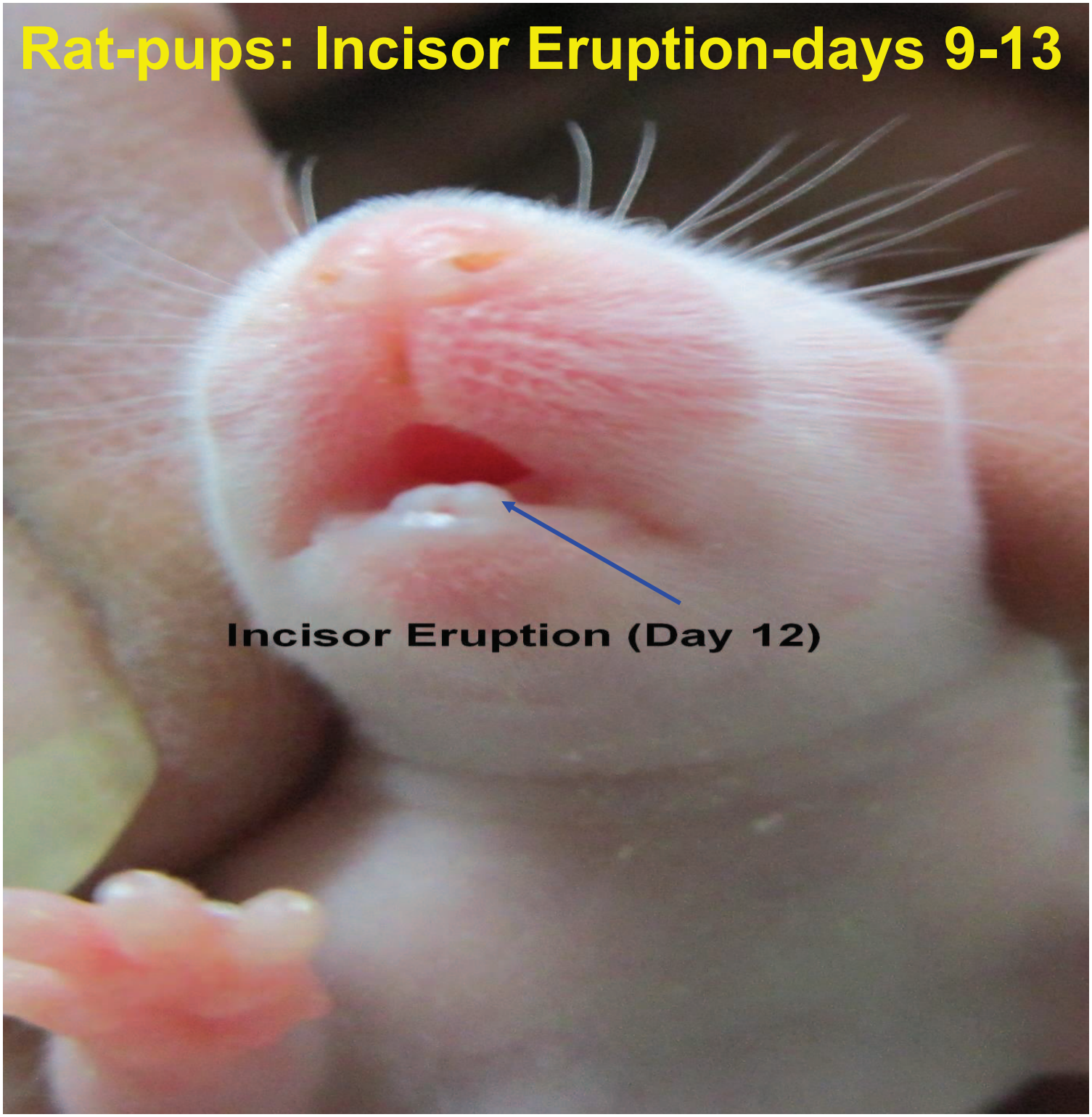
# 1-Day old Rat-pup




Ear pinna- Unfolded (Day 6)
Eye- Closed


Coat Growth (Day 11)

# Rat-pups: Incisor Eruption-days 9-13



# Rat-pups: Eye opening days-12-17

# Role of QA

## What QA is expected to check/audit

- Multiple checks of inhalation exposure units

  e.g. Vacuum, Master flow control, temp and humidity within chamber, fixation of animal-tubes or masks

- Deposits of test item in tubing and its effect on dose delivered

- Uniform distribution of test item from top to bottom ports

- Particle size i.e. D-90 = 5 u

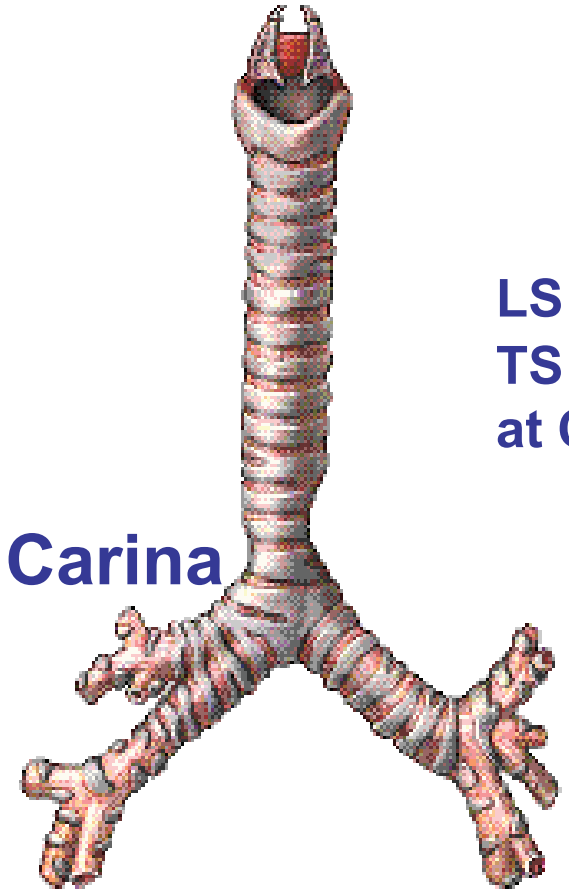
# What QA is expected to check/audit (contd)

- Comparison of gravimetric Vs analytical dose analysis
- Validation of each dose-analysis method
- Confirmation of dose administered/animal
- CoA of test and control items (API : Excipient), expiry dates, storage conditions, stability/re-test date

# What QA is expected to check/audit (contd)

- Verifying of special tissues to included at necropsy
- Especially at least 4 cuts at snout
- Appropriate collection of trachea, main stem trachea, mediastinal lymph nodes
- Lungs inflated with formalin at necropsy.
- All lymph nodes near salivary glands

# Larynx, trachea and bronchi




LS and TS of trachea and TS of bronchi and section at Carina

Thank You