Challenges in Nonclinical Development of Inhalation Drug Products

Luqi Pei, Ph.D.
Senior Pharmacologist
DPARP, CDER

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Disclaimer

This speech reflects the views of the speaker and should not be construed to represent FDA’s views and policies.
Outline

- Characteristics of inhalation drug products (IDP)
- Nonclinical development of IDPs
- Challenges in nonclinical development of IDPs
Inhaler Examples

and much more ...
Nebulizer Examples

and much more …
Complexity of Inhalation Drug Products

DPI (diskus)  Inside of diskus  MDI

Fixed combination: Inhalers
Non-fixed: Nebulizers and drugs

Inside of a MDI
IDPs are complex combinational products

- **Active ingredient**
  - Small molecules
  - Proteins
  - Oligonucleotides
  - Nanotechnology products

- **Formulation**
  - Active pharmaceutical ingredients
  - Excipients
  - Particle sizes
  - Impurities & degradants

- **Device**
  - Inhalers
  - Nebulizers
  - Nasal sprays
  - Intratracheal tubing

- **Drug/device**
  - Dosage forms
    - Dry powders,
    - Solutions
    - Suspensions
    - Gases
  - Leachables & extractables
Human Uses of IDPs

• Indications:
  – Asthma
  – COPD
  – Respiratory distress syndrome (RDS)
  – Pulmonary fibrosis
  – Migraine
  – Diabetes ...

• Use duration
  – Short-term
  – Intermittent
  – Chronic

• ROA
  – Inhalation
  – Instillation
  – Nasal spray
IDP Plus and Minus

Pros

• Direct delivery of drugs to the site of action
• ↑ Drug concentrations at the site of action
• ↓ Systemic absorption and toxicity
• ↑ Safety profile
• ↓ Drug substance material
• ↑ Bioavailability of drugs

Cons

• Device complexity
• Device performance and uniformity
• Demographics-related issues
Stages of Drug Development

- Discovery
- Development
- Registration
- Post-marketing
Components of Drug Development

- Chemistry and Manufacturing Control
  - Drug manufacturing and testing
  - Formulation development
  - Device design and testing
- Nonclinical safety evaluation
  - Active pharmaceutical ingredient
  - Excipients
- Clinical efficacy and safety
  - Phase 1, 2, and 3 trials
Nonclinical safety evaluation

- Pharmacology
- Pharmacokinetics
- Toxicology
  - Acute toxicity
  - Repeat dose toxicity
  - Genetic toxicity
  - Carcinogenicity
  - Reproductive toxicity
  - Special toxicity
Nonclinical safety evaluations of IDPs attempt to make connections between animals and humans

Inhalation toxicity studies

- Help us to understand the toxicity profile of inhaled test articles in animals
  - Systemic toxicity ?
  - Local Toxicity ?
  - Dose-response relationship ?

Nonclinical Safety Evaluations

- To determine whether the toxicity observed in animals are relevant to humans
- To predict toxicity profile in humans
- To prevent unnecessary harm from occurring in humans
Characteristics of Inhalation Toxicity Studies

• Inhalation toxicity studies in animals require special facilities, equipment, knowledge and skills.
• Many factors can affect the results and quality of inhalation toxicity studies. Some of the factors may be applicable to humans.
• Modes of exposure in animals mimic clinical situations to the extent possible.
• Exposure levels (dosimetry) in animals are estimates based on empirical data.
Hardware Needed

- Building specially designed to handle airborne chemicals in the testing settings
- Equipment for generating and characterizing aerosols, particles, gases containing the testing material
- Equipment and device for exposing animals to the aerosols and determining exposure levels
- Equipment to ensure the safety of operating personnel and to prevent contamination of the environment
Inhalation Exposure Systems

Courtesy of Dr. Mathews Reed

Dog

← Rat

Courtesy of Dr. Mathews Reed
Fate of Inhaled Particles

Forbes et al, 2013, Advanced Drug Delivery
Distribution of Inhaled Compounds in Rats & Human Lung

Courtesy of Dr. Mathews Reed
Regional Deposition of Inhaled Particles as a Function of Particle Size in Humans

Species Differences in Deposition of Inhaled Particles in Animals and Humans

Estimating Exposures

- Exposures of animals to drugs in inhalation toxicity studies are estimates using the following formula:

\[
DD = \frac{[C \times RMV \times D \times IF]}{BW}
\]

\[
RD = DD \times F
\]

where:
- DD = Delivered dose (also known as achieved dose or inhaled dose in some reports) in \(\mu g/kg/day\), amount of drug present in the volume of inhaled air
- C = Aerosol drug concentration \((\mu g/L \text{ air})\)
- RMV = Respiratory minute volume \((L/min)\)
- D = Duration of daily exposure \((min/day)\)
- IF = Inhalable fraction \((1 - 5 \mu m \text{ particles})\), most reports do not have this number \(\text{i.e., FR} = 1\) currently
- RD = Regional deposits/exposure \((\mu g/kg/day, \text{ e.g., nasal or pulmonary})\)
- F = Deposition factor for the region of interest
# Respiratory Parameters for Selected Laboratory Species and Humans for Drug Safety Evaluations

<table>
<thead>
<tr>
<th>Species</th>
<th>Body Mass (kg)</th>
<th>Minute Volume</th>
<th>Fractional Pulmonary Deposition (1 - 5 (\mu)m)</th>
<th>Lung Mass (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>L/subject</td>
<td>L/min/kg</td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>0.30</td>
<td>0.04</td>
<td>1.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Rat</td>
<td>0.25</td>
<td>0.20</td>
<td>0.80</td>
<td>0.10</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>0.70</td>
<td>0.46</td>
<td>0.66</td>
<td>0.20</td>
</tr>
<tr>
<td>Monkey</td>
<td>2.4</td>
<td>0.70</td>
<td>0.29</td>
<td>0.25</td>
</tr>
<tr>
<td>Dog</td>
<td>10</td>
<td>3.6</td>
<td>0.36</td>
<td>0.25</td>
</tr>
<tr>
<td>Human</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Responses to Inhaled Materials

• Some chemicals have both local and systemic toxicities while others may have only one of them.
• This presentation discusses the pulmonary toxicity only.
• Types and severity of pulmonary lesions may vary significantly between chemicals, doses, study duration, and animal species.
• Examples of pulmonary toxicity are provided in the next 2 slides.
### Responses of Respiratory Tract in Rats

<table>
<thead>
<tr>
<th>Finding</th>
<th>Sex</th>
<th>Main Study</th>
<th></th>
<th>Recovery</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>LD</td>
<td>MD</td>
<td>HD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0</td>
<td>2 (1) (a)</td>
<td>10 (1.4)</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0</td>
<td>6 (1)</td>
<td>10 (1.6)</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>Larynx, epithelial squamous metaplasia</td>
<td>M</td>
<td>0</td>
<td>3 (1)</td>
<td>4 (1)</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Polymorphonuclear cell infiltrate</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10 (1.5)</td>
</tr>
<tr>
<td>Submucosal duct/gland ectasia</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10 (1.5)</td>
</tr>
<tr>
<td>Lung, ↑ alveolar macrophages</td>
<td>M</td>
<td>2 (1)</td>
<td>4 (1)</td>
<td>6 (1.5) (b)</td>
<td>10 (1.5)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>3 (1)</td>
<td>4 (1.2)</td>
<td>7 (1)</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Bronchiolar inflammation</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Bronchiolar erosion</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Bronchial epithelial hyperplasia</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

\(a\). Laryngeal squamous epithelial metaplasia is a species-specific response to inhaled materials in rodents.

\(b\). Increases in in the incidence and severity of alveolar macrophages in the absence of other findings (see HD group) are of little safety concern.

\(c\). It appears reasonable to consider the mid dose (MD) as the NOAEL.
Lung Pathology in Monkeys

Inhaled Drug X (twice/week for 13 weeks)

- 0.00 mg/kg
- 1x mg/kg
- 2x mg/kg
- 4x mg/kg
Species Differences
in Anatomy & Physiology of the Respiratory System

• Nose
  – Rodents have more complex nose structures.
  – There are species differences in the nasal metabolic enzymes. (e.g., roflumilast-related nasal lesions in rodents)

• Larynx: Rodent larynx are prone to develop laryngeal squamous metaplasia.

• Airways: Relatively minor, but some locations may not be relevant (e.g., nasal response in an orally inhaled drug)

• Pulmonary region: No special consideration needed
Challenges

• Lack of guidance in design and conduct of inhalation toxicity studies of inhaled drugs
  – Both EPA and OECD guidelines may be inadequate.

• Lack of understanding of the complexity and special technique requirements of inhalation toxicity studies

• Lack of understanding of the special characteristics of respiratory response to inhaled drugs and route-specific findings
Challenges (2)

- Drug-related responses identified in nonclinical studies are generally considered clinically un-monitorable
- Differences in opinions in interpreting scientific findings
- Cost
Summary

- IDP development is unique due to the complex characteristics of drug products and inhalation toxicity studies in animals.
- Inhalation toxicity studies generally evaluate both local and systemic effects of compounds of interest while non-inhalation studies do not adequately evaluate the pulmonary effects of the compounds.
- Part(s) or all of the respiratory system may be exposed to the drugs in inhalation toxicity studies in animals.
- Animal exposures to inhaled drugs are estimates that are subject to a number of conditions: particle sizes, aerosol drug concentrations, exposure duration, minute volume, and deposition factor based on selected animal species.
Contact Information

Luqi Pei, Ph.D.
Senior Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Products

Luqi.pei@fda.hhs.gov
Tel.: 301-796-1269