FDA Expectations and Evaluation of Inhalation Toxicology Studies

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Development of inhalation products has unique regulatory aspects

My primary goals today are to

- Review the FDA nonclinical expectations for inhalation drug development programs
- Discuss key evaluation aspects of inhalation studies including dose calculation and clinical dosing
- Discuss toxicities of concern by IH route
What Makes the Development of Inhalation Products Unique?

- Generation and characterization of aerosol or dry powder formulations
- Delivery of drug directly to a critical organ
  - increased potential for pulmonary toxicity
- Dose calculation @ FDA considers pulmonary deposition in nonclinical models
There are some basic nonclinical requirements for respiratory drug development

- **Pharmacology**
  - Pharmacodynamics
  - Safety pharmacology

- **Toxicology**
  - General toxicology
  - Genetic toxicology
  - Carcinogenicity
  - Reproductive and developmental toxicology
  - Juvenile development
  - Special toxicology
  - Toxicokinetics

- **ADME**
There are some basic nonclinical expectations for inhalation toxicology studies

- Conduct according to GLP
- Clearly described methodology
- Adequate duration to support proposed clinical trials (ICH Guidance M3(R2))
- Submit at least draft report with line listing of data to support proposed clinical trial
There are some basic nonclinical expectations for inhalation toxicology studies (2)

- Appropriate study design
- Adequate dose selection
- Adequate particle size and dose characterization
There are some basic nonclinical expectations for inhalation toxicology studies (3)

- Species selection
  - as for other routes, usually 2 species, at least one non-rodent

- Route of exposure
  - IH
  - IH + other (if systemic exposure insufficient with IH alone)
There are some basic nonclinical expectations for inhalation toxicology studies (4)

- **Study design:** often 2 types of controls
  - sham/air
    - especially useful if vehicle is novel
  - vehicle

- **Modes of exposure**
  - rodents: nose–only
  - non–rodent: face mask or oropharyngeal tube
ADME and TK Take on Added Importance for Inhalation Products

- For drugs intended to treat pulmonary diseases
  ◦ ideally desire systemic exposure to be minimal (e.g., corticosteroids)

- For drugs designed to treat systemic diseases
  ◦ confirm systemic exposure
  ◦ measure rate of absorption if IH route chosen for rapid onset of action (e.g., diabetes, migraine drugs)
US FDA “considerations” for nonclinical programs for respiratory products are available

  - published by members of the then Division of Pulmonary Drug Products, Center for Drug Evaluation and Review
FDA publication discusses aspects of starting clinical dose selection

- Initial clinical dose is generally a fraction of the NOAEL in animals
  - < 1/10 the NOAEL in rats or 1/6 the NOAEL in dogs on a mg/kg BW basis

- Other adjustments may be appropriate

- Dose comparisons may also be based on body surface area
  - smaller safety factors are appropriate
The FDA publication provides some advice regarding dose extrapolation

- PK information useful for making comparisons between preclinical and clinical exposures
  - requires previous human experience
  - without PK data, preferable to use dose comparisons based on body surface area
  - BW comparisons appropriate when toxicities occur at similar mg/kg doses across species
However, the publication does not address all relevant issues

- The FDA publication does **not** address
  - pulmonary dose calculation in the animal studies
  - extrapolation to clinical doses based on the calculated deposited dose
    - especially important since goal is often to avoid significant systemic exposure
Dosimetry calculations for inhalation studies can be complicated

- Dosing is usually a theoretical estimate

- Dose varies with
  - mode of exposure (nose only vs oral inhalation)
  - particle size
  - anatomic location
    - pulmonary
    - extrathoracic
    - intranasal

- Important QC aspect of study report
Pulmonary deposited dose is calculated by the following formula

Dose (mg/kg/day) = \(\frac{C \times T \times RMV \times DF}{BW}\)

Where:

- \(C\) = drug concentration (mg/L)
- \(T\) = duration of exposure (min/day)
- \(RMV\) = respiratory minute volume (L/min)
- \(DF\) = pulmonary deposition factor
- \(BW\) = body weight (kg)
The individual factors are measured or estimated

- C, T and BW can be measured directly

- RMV is either measured directly or estimated – (most estimate)
  - estimates typically reference equations from a few publications
    - $0.608 \times BW^{0.852}$; Alexander et al, Inhal Tox, 2008
    - $0.499 \times BW^{0.809}$; Bide, RW et al, J Appl Toxicol, 2000
  - estimates based on allometric comparisons may underestimate RMV by up to 40% (Sweeney, 2007)
The individual factors are measured or estimated (2)

- DF is estimated based on particle size characteristics

- Ideal particle profile has MMAD of 1 – 4 $\mu m$ to allow for pulmonary deposition
  - Note: too large a MMAD can invalidate study

- DF is typically 0.1 for rodents and 0.25 for non-rodents
Pulmonary deposition profile differs across species

Wolff and Doratto, 1993
The pulmonary deposited dose in the rat can be calculated as follows:

- Dose (mg/kg/day) = \( \frac{C \times T \times RMV \times DF}{W} \)

\[
(0.5 \text{ mg/L} \times 60 \text{ min} \times 0.325 \text{ L/min} \times 0.1) \div 0.25 \text{ kg} =
\]

Pulmonary deposited dose of 3.9 mg/kg
Local pulmonary responses are often observed

- Responses in the respiratory system include cellular infiltration and tissue lesions (epithelial degeneration, ulceration/erosion, necrosis)

- Considered non-monitorable in the clinic in a population that is usually already compromised

- Often dose-limiting toxicity
Local pulmonary responses are often observed (2)

- Nasal lesions produced by drug intended for oral inhalation administration in clinic usually not considered in safety evaluation

- Laryngeal squamous metaplasia in rodents considered rodent specific finding
Certain considerations may help to address pulmonary toxicities

- Do longer term studies show progression of lesion?
  - Inflammatory cell infiltration progressing to epithelial lesions
  - Increasing severity with dose/duration
- Reversible?
- Historical control data?
- Are similar findings observed in studies conducted with approved products?
Acceptable clinical doses based on evaluation of local and systemic effects

- Of local and systemic effects, the pulmonary system is usually the most sensitive
  - NOAEL for local and systemic effects may differ

- Dose selection for a proposed clinical trial is typically based on the pulmonary deposited dose at the NOAEL
There are 2 aspects for systemic effects in selecting clinical doses

For identified **systemic** effects:

- **Safe starting** dose calculated as per FDA’s Guidance for Industry (2005) based on BSA comparisons
  - Calculate human equivalent dose (HED) and incorporate safety margin

- **Maximum** dose generally set on a mg/kg or exposure (AUC) comparison basis with inclusion of appropriate safety margins
There is 1 primary consideration for local effects in selecting clinical doses

For identified pulmonary effects:

- Maximum dose set on a mg/kg BW or mg/g lung weight comparison with inclusion of appropriate safety margins
  - typically 10 for rodents, 5–6 for non–rodents
Overall clinical dose selection considers both effects

- The maximum accepted clinical dose is based on the more conservative of the two evaluations in the most appropriate of the species tested
  
  - Note: deposition in humans is assumed to be 100% of the administered dose
Consider the following case example

14-day rat inhalation study

- Pulmonary deposited doses of 0, 1, 5, and 25 mg/kg

- NOAELs:
  - **Pulmonary**: 1 mg/kg based on inflammatory changes & epithelial degeneration at 5 mg/kg and above
  - **Systemic**: 5 mg/kg based on kidney tubular necrosis at 25 mg/kg
Consider the following case example (2)

- **Pulmonary NOAEL supports maximum clinical dose of ~ 16.5 mg**
  - \[1 \text{ mg/kg } \times 0.25 \text{ kg (rat BW)} / 1.5 \text{ g (rat lung wt)} = 0.165 \text{ mg/g}\]
  - \[0.165 \text{ mg/g } \times 1000 \text{ g (human lung wt)} / 10 \text{ SF} = 16.5 \text{ mg}\]

- **Systemic NOAEL supports maximum clinical dose of up to 25 mg based on BW comparisons**
  - \[5 \text{ mg/kg } / 10 \text{ SF } \times 50 \text{ kg person} = 25 \text{ mg}\]

*: supporting dose could be modified with systemic exposure data*
Consider the following case example (3)

- Therefore, the rat study supports clinical dosing for 14 days at doses up to 16.5 mg/day

- Similar evaluations typically needed in a non-rodent study

- Most appropriate specie is used for ultimate clinical dose selection
Not all FDA drug review divisions follow the described approach

- Division of Special Pathogen and Transplant Products
  - dose comparisons based on pulmonary dose levels and lung organ weight are based on assumptions and are not the best approach – doses will be approximations
  - a better surrogate for pulmonary exposure is systemic exposure measured by AUC values provided that AUC values are calibrated with AUC values for discreet IV doses
Thank you for your attention!