Nonclinical Safety Evaluation of Inhalation Drug Products

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Overview

• Introduction
• Toxicology
• Pharmacology
• Inhalation toxicity studies
Introduction to Inhalation Drug Products

Inhalation Drug Products:
- Inhalation: an increasingly popular route of drug delivery
- Indicated for:
  - Diseases of the respiratory system
  - Other systems (e.g. insulin for diabetes)
- Using devices: metered-dose inhalers, dry powder inhalers, and nebulizers
- Safety evaluation consists of:
  - Clinical
  - Nonclinical
  - Manufacturing controls
Scope of Nonclinical Program

- **Toxicology**
  - General toxicity
  - Genetic toxicity
  - Carcinogenicity
  - Reproduction and developmental toxicity
  - Special toxicity
  - Toxicokinetics

- **Pharmacology**
  - Pharmacodynamics
  - Safety pharmacology
  - Pharmacokinetics

- **Compounds of Interest**
  - Active ingredients
  - Excipients
  - Formulation
    - Interaction of mixtures
    - Impurities, degradation products, extracables and leachables
Regulatory Guidelines for the Nonclinical Safety Evaluation of Inhalation Drug Products

• Considerations for Toxicology Studies of Respiratory Drug Products.
  – DeGoerge et al., Regul Toxicol Pharmacol, 1997;25:189-193

• ICH guidelines:

• FDA guidelines (ICH guidelines plus documents listed in the following site):
  – http://www.fda.gov/cder/guidance/index.htm - Pharm/Tox
II. Toxicology

1. General Toxicity Studies

• Guidance
  – (ICH) S3B: Pharmacokinetics: Guidance for Repeat-Dose Tissue Distribution Studies
  – (ICH) S4A: Duration of Chronic Toxicity Testing in Animals (Rodent and Non-rodent Toxicity Testing)

• Studies:
  – Include at least two species (≥ 1 non-rodent species)
  – Use inhalation (IH) route of administration or IH + non-IH
  – Expose animals daily
  – Treatment duration is up to
    • Six months in rodents
    • One year in non-rodents
  – Evaluate both local and systemic toxicities
2. Genetic Toxicity Studies

• Guidance
  – S2A: Specific Aspects of Regulatory Genotoxicity Testing for Pharmaceuticals
  – S2B: Genotoxicity: A standard Battery for Genotoxicity Testing for Pharmaceuticals

• Program
  – Three tests suffice if they give no signal of concern
    • Bacterial mutagenicity test
    • \textit{in vitro} chromosomal aberration test
    • \textit{in vivo} chromosomal aberration test
  – More tests may be recommended otherwise
3. Carcinogenicity Studies

- **Guidance (ICH):**
  - S1A: The Need for Long Term Rodent Carcinogenicity Testing of Pharmaceuticals
  - S1B: Testing for Carcinogenicity of Pharmaceuticals
  - S1C: Dose Selection for Carcinogenicity Studies of Pharmaceuticals
  - S1C(R): Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals

- **Program**
  - Bioassays in 2 species
  - Protocols subjected to FDA’s review and approval
4. Reproductive & Developmental Toxicity Studies

• **Guidance**
  - (ICH) S5A: Detection of Toxicity to Reproduction for Medicinal Products
  - (ICH) S5B: Detection of Toxicity to Reproduction for Medicinal Products: Addendum on toxicity to Male Fertility
  - (FDA): Nonclinical Safety Evaluation of Pediatric Drug Products

• **Non-inhalation route of administration may be acceptable**

• **Use inhalation exposure for juvenile animal studies**
5. Special Toxicity Studies

- Tissue irritability/compatibility
- Respiratory hypersensitivity
- Immunotoxicity
- Others
6. Toxicokinetics Studies

• Component (usually) of toxicity studies
• Monitor plasma levels and AUCs of the drug and its metabolites
• Evaluate both dose proportionality and temporal effects of exposure
• Guidelines
  – (ICH)S3A: Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
III. Pharmacology

- **Pharmacodynamics**
  - Receptor binding and activation
  - Enzyme inhibition and activation
  - Mechanism of drug action
  - Efficacy studies
    - *in vitro*
    - *In vivo*
  - Drug interactions

- **Safety pharmacology**

- **Pharmacokinetics (ADME)**
IV. Abbreviated Nonclinical Program

• Consists of only parts of the above nonclinical program

• Is applicable to:
  – New drugs with short-term clinical use
  – Well-known drugs or excipients when:
    • Reformulation
    • New route of administration
V. Inhalation Toxicity Studies

- Should be in compliance with GLP regulations
- Have five steps process
  - Protocol development
  - Conducting the study
  - Protocol amendments
  - Drafting study report
  - Auditing and finalizing the report
Exposure System of Inhalation Toxicity Studies
Characteristics of Inhalation Toxicity Studies

• Design
  – Modes of Exposure
    • Nose-only
    • Oral inhalation
  – Needing controls and treated animals

• Dosimetry

• Toxicological Evaluation
  – Systemic toxicity: similar to other studies
  – Local toxicity: more detailed evaluations
Inhalation Toxicity Studies - Design

• Have Generally five groups
  – Sham control (air, or saline)
  – Vehicle control
  – Testing Groups
    • Low dose
    • Mid dose
    • High dose
• Include Both sexes / treatment
• Use extra animals /dose for TK (rats, mice)
Samples of Inhalation Exposure Chambers in Toxicity Studies
Dosimetry of Inhalation Toxicity Studies

- Is a theoretical estimate

- Varies with mode of exposure, particles size, species and anatomic location (indications)
  - Local drug depositions / concentrations
  - Plasma drug levels

- Needs stringent quality controls
Deposition of Nasally Inhaled Aerosol Particle in Humans
Effect of Species and Mode of Exposure on Pulmonary Drug Deposition
Exposure Assessment

Dose (mg/kg/day) = \( \frac{C \times T \times M \times F}{W} \)

Where:
- \( C \) = Aerosol drug concentration (mg/L)
- \( T \) = Duration of exposure (min/day)
- \( M \) = Minute volume (L/min)
- \( F \) = Deposition factor
- \( W \) = Body weight (kg)
Endpoints for Toxicological Evaluation

- Dosimetry
- Systemic toxicity
- Local toxicity
Dosimetry Evaluation

- Characterization of the exposure system
- Particle size distribution
- Dosing variations
- Deposition factor used
- Dose estimates
Endpoints for Evaluating Systemic Toxicity

- Clinical observations
  - Mortality
  - Food and water consumption
  - Body weights and body weight gains
  - Any abnormal signs and behavior
  - Ophthalmology
  - EKG and other evaluations

- Clinical pathology
  - Hematology
  - Serum chemistry
  - Urinalysis

- Necropsy
- Histopathological examinations
Endpoints for Evaluating Local Toxicity

• Functional changes
  – Plethysmography
  – Lung mechanics
  – Gas diffusing efficiency

• Biochemistry changes

• Morphological changes
  – Non-neoplastic changes
  – Neoplastic changes
Summary

The nonclinical safety evaluation of inhalation drug products:

- Is a part of the overall safety evaluation that:
  - Also includes clinical and CMC disciplines
  - Incorporates risk/benefit analysis
- Consists of toxicology, pharmacology, and pharmacokinetics
- Includes the evaluation of the formulation and its components
- Needs inhalation toxicity studies that
  - Examine local and systemic toxicities of the drug
  - Tend to have large variations in their dose estimates
  - Have body burden estimates based on indications
- Varies with drugs and their indications in nonclinical requirements
Clinical Considerations for Inhalation Toxicities

- **Short-term considerations (tolerability)**
- **Done immediately post-first exposure(s):**
  - Tolerability in Normals first
  - Testing in vulnerable populations (e.g., asthmatics)
  - Assessed by AEs, Serial Spirometry (+/- oximetry)
  - Applies for new drug substance and/or novel excipient
Clinical Considerations for Inhalation Toxicities

• Long-term considerations (pulmonary safety)
  – Work-up / testing level and duration partly depends on pre-clinical toxicology work/expectations
  – “Complete” work-up could include:
    • Full Pulmonary Function Testing (including lung volumes, diffusion capacity, +/- Pulmonary Exercise Testing, +/- methacholine challenge)
    • Radiography (most sensitive assessment is with high-resolution CT scanning)
    • Pulmonary Adverse Events, examination, ...
Clinical Considerations for Inhalation Toxicities

• Long-term considerations (pulmonary safety)
  – Duration of testing dependant on expected duration of exposure
  – If chronic and/or episodic but likely frequently recurrent
    • >= 1 year of testing is expected
  – Likely limited exposures would require less exposure duration
  – “N” - ICH for New Molecular Entity - 1500 total exposures, 300 patients for 6 months, 100 for 1 year (similar target for important new excipient by inhalation not unreasonable)