INHALED PHARMACEUTICALS:

Comparing Approaches for Small and Large Molecules

Whether you are developing a new chemical entity (NCE) (small molecule) or biopharmaceutical (large molecule) to be dosed by the inhaled route, there are some key aspects of your compound that should be well understood. Some of these will be similar for both NCEs and biopharmaceuticals, while others will differ for these products. Covance's experts have highlighted a number of shared considerations for inhaled products as well as some specific considerations for biopharmaceuticals.

SHARED APPROACH

- Need proof of drug exposure by measuring drug levels (toxicokinetics) in blood and/or bronchoalveolar lavage
- Dosing methodology and aerosol generation techniques
- Lung deposition for a given particle or droplet size
- Same target article size range
- Deposited dose vs delivered dose calculations
- Aerosol concentration characterisation and determination requirements
- Pathology endpoints
- Measurement of bodyweights, food consumption and clinical observations
- Animal species and strains
- Use of macro and microscopic pathology, clinical chemistry and hematology
- Similar formulation composition
- Range of delivery solutions available, including customer clinical devices

Covance offers customers the largest, most experienced and fully integrated inhalation contract capability globally

With over 60 purpose-designed and built exposure suites dedicated to inhalation studies, we provide expertise and capabilities in the following areas:

- Global operation with harmonized procedures and equipment
- Extensive experience in study design and data interpretation for respiratory and systemic disease targets
- Test item conserving methods and study designs
- Unique in-house engineered solutions
- Animal welfare focus
- Regulatory submission consultancy

LARGE MOLECULE SPECIFICS

- Improved target identification means less susceptible to off-target and secondary pharmacology
- Assessment of pharmacodynamic endpoints should be included where possible
- Additional biomarkers and assays required dependent on the specific biology of each product
- Dose limitation likely to be based on practical methodology and formulation rather than toxicity
- Extent of safety pharmacology assessments determined by product biology
- Increased potential for immunogenicity by the inhaled route. Characterized to better understand PK/PD
- Most inhaled biopharmaceuticals are first-in-class, therefore compound comparison will be less likely
- Bioanalysis typically by ligand binding assay (ELISA/MSD/Gyrolab), LC-MS/MS can also be utilized for certain product modalities such as peptides and oligonucleotides
- Inclusion of an activity assay to confirm test item potency is not inhibited by aerosolization
- Product development typically follows ICH S6 guidelines
  - Pharmacologically relevant species will be required for all studies
  - Progress only one species in longer term sub-chronic and chronic studies or if only a single relevant species can be identified
  - Carcinogenicity risk assessment usually negates the requirement to perform 2-year studies
- Most biopharmaceuticals are developed as liquid formulations
- Fixed formulation strength common to ensure optimum test item stability
- Extent of lung absorption may be affected by size of the biopharmaceutical or the intended biology

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