Supporting Inhaled Drug Development

Pulmonary drug delivery offers a non-invasive method to administer therapies that act locally in the lungs or distribute to the circulation to act systemically. Pulmonary delivery is achieved by oral inhalation, where a drug product is breathed through the lungs and enters into circulation via alveolar epithelium or through intranasal administration.

For all candidate drugs that are to be administered by inhalation, pulmonary safety and tolerability will need to be evaluated, while systemic exposure usually needs to be investigated as part of investigating (systemic) safety and efficacy. In the case that a drug was previously developed for administration through another route, the adequacy of inhaled drug administration will often need to be compared to the original product.

Moreover, the device and formulation applied for pulmonary delivery of (new) candidate drugs may change early during clinical development, for instance from a nebulized dosage form for exploratory research to a to-be-marketed product using a commercial Dry Powder Inhaler. Any such product changes require that bioequivalence of old and new drug product shall be confirmed.

Pulmonary Drug Delivery Offers:

- A non-invasive delivery method
- A preferred administration method for patients with respiratory disease (e.g. asthma, COPD) or lung cancer
- The ability to treat the symptoms right at the site or target lung cells
- A user-friendly route of administration for systemic delivery as compared to needle injections
- An administration helping to avoid first-pass metabolism

Pharmacokinetic (PK) Considerations for Inhaled Drugs

Following pulmonary administration, systemic and local drug PK is assessed to determine bioavailability.

- **For drugs targeting the lungs:** plasma PK is critical for judgment of systemic exposure and safety, however, for inhaled products with limited systemic exposure bioanalysis of plasma PK can be challenging in perspective of assay limits of detection.
- **For systemically acting drugs:** assessment of PK is crucial for confirming whether adequate levels of drug can be established through this administration route.

Pharmacodynamic (PD) Assessments Following Drug Inhalation

Biomarkers in sputum, bronchoalveolar lavage (BAL) fluid or exhaled breath matrices, can provide insight into whether drug delivery to the lung following inhalation is effective and safe. Successful bioanalysis of collected samples depends on appropriate sample collection, sample handling and fit-for-purpose assays with the required tier of validation.

Device Considerations

The administration device will depend on the drug's physicochemical properties, stage of development and (anatomical) location of the drug target. Types of devices can be selected for inhaled drug delivery include:

- **Dry Powder Inhalers**
  - Single-dose reusable
  - Multi-dose
  - Single-use
- **Pressurized Meter-Dose Inhalers (pMDI)**
- **Breath-Actuated Inhalers**
- **Nebulizers**
- **Nasal Sprays**

Inhaler devices for clinical testing in humans must be in conformity with locally applicable Medical Device Regulations (MDR). Switching inhalation device (and formulation) during the course of drug development may require bridging studies to confirm bioequivalence.

Patient Instructions and Dose Monitoring

- Participant inhaler/device training is integral to study success
- In-house monitoring of dose administration is critical for Phase I PK studies
- Appropriate dosing and well-timed sample collection is key for PK and PD evaluation

Celerion's Respiratory Medicine Experience

Celerion is a global leader in respiratory studies. Our Belfast, UK clinic has decades of proficiency with highly specialized assessments in the field of respiratory medicine. With a plethora of experience conducting Phase I/II studies involving novel drug treatments for mild to moderate and severe asthma, chronic cough, COPD and cystic fibrosis.

Why Choose Celerion Belfast, UK for Respiratory Medicine?

- MHRA-accredited clinic with 78 beds across 4 clinical wards
- Specialist clinicians with > 10 years experience in inhaled drug studies
- On-site clinical safety laboratory with rapid turnaround time
- Respiratory suite offering a full complement of respiratory assessments including diffusing capacity for carbon monoxide (DLCO), spirometry, body plethysmography and fractional exhaled nitric oxide (FeNO)
- Bronchoscopy suite allows BAL to be performed within the clinic
- Inhaled dosing rooms with extraction
- Enrollment of exploratory patient cohorts within 4 respiratory disease areas: asthma, chronic cough, COPD and cystic fibrosis
- Experience with challenge tests (LPS, methacholine, adenosine, tussigenic agents etc.)

Case Study

NEED: A biotech company was developing an inhaled peptide drug to be administered by nebulization. The client was seeking a full service CRO with extensive experience with inhaled products.

APPROACH: In a collaborative process, the Celerion Protocol Writing team worked closely with the sponsor to develop a protocol to assess drug PK/PD.

- Pulmonary function was assessed by spirometry prior to and post-drug administration.
- Bronchoscopy was performed to collect bronchial lavage fluid for PK and lung microbiome determinations.

BENEFIT: Efficient study conduct with in-house expertise and on-site specialized equipment

- Celerion has extensive experience with inhaled products, including peptide drugs
- Our Belfast, UK clinical pharmacology unit is equipped with a dedicated bronchoscopy suite for BAL fluid sampling and specialized spirometry equipment.
- Patient safety was tightly monitored by clinical team and supported by an on-site fully-dedicated clinical laboratory
- Timing of PK sample collection and PD assessments was selected on anticipated PK properties of study drug (and its metabolites) following inhaled administration (e.g. time to Tmax, half-life)

RESOURCES:

Respiratory Disease Expertise

Belfast Fact Sheet

LC-MS/MS Assay Method Development (with a Reduced LLoQ) for Inhaled Albuterol

Pulmonary Sampling Techniques and Analysis

Immune Challenge Models