

## API Sparing Techniques for Inhalation Toxicology Studies

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### Avoiding Delays From Limited API

Early pharmacokinetic (PK) inhalation studies must be conducted to ascertain the appropriate dose for preclinical studies leading to investigational new drug (IND) submissions. These preclinical studies often require large quantities of active pharmaceutical ingredient (API) due to the inherent inefficiencies of inhalation dosing; only a small percentage of a drug actually reaches the lungs compared to the amount required to generate the inhalation atmosphere in a typical inhalation exposure chamber system. Often, API available can be limited due to small-batch manufacturing, high manufacturing cost or complexity, or low-yield synthesis schemes. This paper describes API-sparing techniques for conducting inhalation dosing to complete these early PK studies.

### Inhalation Delivery in High Demand

Drug delivery via inhalation has been the route of choice for the treatment of respiratory disease since the introduction of specialized inhalation devices such as the metered dose inhaler in 1956.<sup>1</sup> Inhalation administration has several advantages, chief among them being delivering medications directly to the site of action—the lungs (the organs primarily affected in respiratory diseases)—and bypassing the first-pass metabolism inherent with other routes of administration. Consequently, a medication's potential side effects are reduced since the systemic exposure to the drug is secondary compared to the drug levels in the lung tissue, the required site of action.

The development of inhaled medications for respiratory diseases remains an active area in pharmaceutical drug development. As the population ages, the number of individuals affected by respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and lung



Figure 1. Dry powder and metered dose inhaler devices.

infections will continue to grow, and the demand for effective therapies will increase accordingly. Inhalation is also being explored as a potential non-invasive route for systemic delivery of protein therapeutics, such as insulin or biologics, due to the lungs' vast surface area, in an effort to replace injections.<sup>2</sup>

### PK Studies on the Path to IND

The path to IND submission for drug candidates must include pharmacokinetic studies at several phases: early efficacy studies in an animal model, preclinical inhalation toxicology studies, and formulation analysis before Phase I clinical trials. Inhalation studies are also employed in formulation optimization studies to identify formulations with the best absorption profiles. The results of these studies are used to determine dose proportionality and bioavailability in early PK screening studies.

One challenge for conducting studies with inhaled drugs is that only a fraction of the inhaled dose deposits in the lungs, requiring the administration of more drug product to achieve the intended dose compared to the more common oral or IV routes. The fraction of inhaled dose that is deposited in the lungs is affected by the aerodynamic size of the aerosol

particles. Moreover, aerosolization efficiency and aerosol properties depend primarily on the physical and chemical properties of the test formulation. For small animals (rodents), the amount of dose deposited is typically only 10% of the dose inhaled but can be as high as 25% for a larger animal. As a result, inhalation administration requires significantly more API to achieve the intended dose.

## Manufacturing Factors Limiting API

Preclinical drug manufacturing efforts ideally provide sufficient API or drug substance for preformulation, analytical and bioanalytical methods development and validation, metabolism and pharmacokinetics, toxicology (both safety and genetic toxicology), and possibly safety pharmacology. However, these early manufacturing batches may produce only small quantities of a drug, creating the need to conduct studies with very minimal amounts of API. In addition, the API may be expensive or difficult to manufacture, also limiting its availability. For inhalation administration studies, it is important to understand factors affecting the API requirements and how to design studies using the API most efficiently to avoid delays resulting from the need to manufacture more API before moving forward with preclinical PK and toxicology studies.

## Greater API Use by Inhalation Studies

Inhalation studies with rodents typically use a flow-past nose-only inhalation exposure chamber consisting of a number of animal ports, with one animal placed in each of the ports. Study animals are held in clear plastic restraining devices (holding tubes) attached to the chambers at the ports, and the test atmosphere flows out of each supply port past the animal's nose. Each port provides both a supply and an exhaust to remove the excess aerosol and expired breath from the animal. For large animals, test article administration is accomplished by custom-fitted face masks. In either case, typically flow rates approximating twice the animal's minute volume (the volume of air inhaled per minute) are supplied at each port.

Combined with the particle deposition efficiency constraint and the need for excess flow rates, about 90% of the API aerosol generated ends up in the exhaust. Though the test

article in the exhaust can be collected for reuse in some cases, it is usually not recommended due to extraneous questions regarding test article stability and integrity.

## Conserving API: Inhalation PK Studies

Alternatively, for the maximum conservation of API during an inhalation study, animals can be manually dosed using specialized delivery devices which deliver aerosols directly to the trachea, bypassing the nasal cavity and larynx. Test animals are anesthetized and drug is administered through the device's rigid tube extending into the trachea of the animal. The required quantity of API is loaded into the reservoir of the dispenser and dispersed as an aerosol plume into the lungs.

This procedure mitigates the need to generate large quantities of test atmosphere and thus the requirement for increased amounts of API. Additionally, since the aerosol is delivered directly to the closed space of the lungs, it improves the deposition of particles and minimizes loss. However, given the need to anesthetize animals undergoing this procedure, this method is best suited for studies requiring single-dose administration or a dosing regimen with multiple days of rest in between.

Intratracheal administration of aerosols yields improved dispersion of the drug into the lungs compared to intratracheal instillation (IT) in which the drug is delivered in bulk as a droplet in the trachea, resulting in hot spots at the sites of deposition and leading to local inflammation and poor absorption. Intratracheal aerosol dosing allows for normal dispersion occurring via breathing, while also conserving the amount of API used.

## Summary

In summary, single dose inhalation PK studies to determine dose proportionality and bioavailability, or for formulation optimization are an important step on the path to IND submission. Standard methods of inhalation administration typically require an excess of API; however, preclinical drug manufacturing batches may provide limiting amounts of API due to an expensive and/or difficult manufacturing processes. Where API is limited, use of intratracheal administration of

aerosols for drug delivery directly to the lungs for inhalation PK studies is a viable alternative both for conserving API and delivering higher quantities of aerosolized drug to the lung.

## About Narayanan Rajendran, PhD

Narayanan Rajendran, PhD, is the Manager of the Inhalation Toxicology Division at IITRI. Dr. Rajendran received both a MS and a PhD in Engineering Sciences (Aerosol Science) from the State University of New York, Buffalo, NY. His research interests are in the areas of aerosol generation and monitoring for inhalation toxicology studies, aerosol kinetics, fluid dynamics, and the pulmonary deposition of particles. He has designed and developed various aerosol/vapor generation systems for inhalation toxicity studies that employ powder dispensers, metered-dose inhalers, and flash evaporators. Dr. Rajendran has published more than 60 research papers, abstracts, and patents, and holds numerous patents in the areas of inhalation toxicology, pulmonary deposition, aerosol science, filtration, and particle generation and monitoring.

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