Inhalation Sciences

More predictive power in pharmacokinetics

A novel tool for generating and depositing aerosols in precise, repeatable, controlled doses

White Paper

Precision dosing: A unique methodology

Control your aerosol Control your dose Control your outcome

Contents

"I broke with conventional dry powder technology — PreciseInhale is the only platform offering precision dosing!".

Dr Per Gerde, CSO

Two core features

#1

PreciseInhale utilizes aerosols from 3 different generator sources: 1) Micronized powder directly, 2) Test aerosols from clinical inhalers 3) Spray aerosols from nebulized liquids. Following aerosol generation, a fine, free-flowing stream of particulate aerosol can be dispensed to a range of alternative exposure modules.

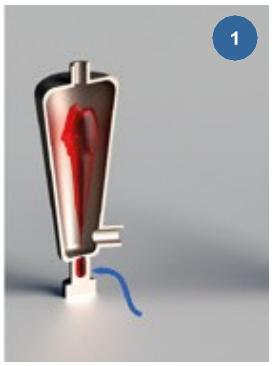
#2

PreciseInhale's software monitors and dispenses the desired target doses of aerosol in real time. Automated software and a light-scattering device measures breathing pattern and the aerosol concentration in real time. This enables researchers to customize their aerosol to their exact needs with consistent particle size distribution that upon exposures provide detailed PK data, including curves with Tmax and Cmax data.

What is precision dosing?

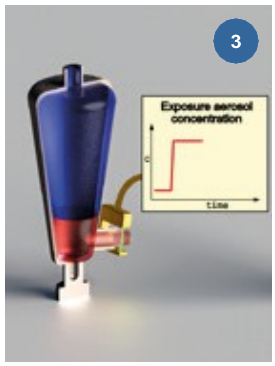
PreciseInhale aerosol generator is built around a methodology called ‘precision dosing’. Using adjustable air pressures and flow rates, settings can be optimized to generate aerosols for precise dosing. Aerosols can be sourced from dry powders, clinical inhalers or nebulized solutions.
The optimized aerosol has a sufficiently reduced particle agglomeration to give a suitable Mass Median Aerodynamic Diameter (MMAD) as determined by the Particle Size Distribution (PSD). When using micronized powder of drugs in development, as little as 100 milligrams of costly test substance can be enough to run a full PK study, compared to 100 g using conventional methods. Generated aerosols constitute a free-flowing, fine particulate air stream that can be controlled for used in a wide range of exposure settings. It produces precise, predictive data with low Standard Deviation.

How does it work?

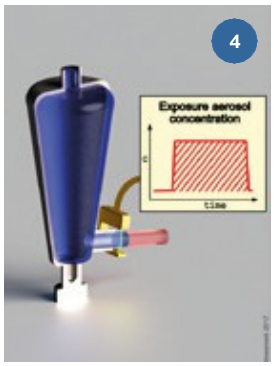


When sourced from micronized powder or clinical inhalers, a cloud of aerosol is generated upwards into the holding chamber.

The aerosol can then be displaced downwards in the holding chamber using a delivery air flow. The test aerosol passes a real-time aerosol monitor before entering the chosen exposure module.



The exposures are monitored and controlled by measuring both air flow and aerosol concentration in real-time.



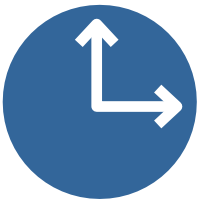
Aerosol concentration, lung ventilation and dose levels are logged to file for each completed exposure.

Benefits

A quality-not-quantity methodology

The precision dosing methodology creates substantial benefits from working on a meticulous scale. Tailoring each exposure, and using small and precise amounts of substance, one-animal-at-a-time, generates exceptionally accurate, reliable results—reducing the number of tests needed, and the amount of test substance required.

As little as 100 mg or less of test substance can run a full PK study.



PreciseInhale® reduces development time by identifying the right candidate drug early on.

Generates data on precise dosing with a typical standard deviation of less than 10%.

The same aerosol is used across the chosen combination of exposure modules producing predictive, comparable data, with less translational issues.

Customized dose setting gives consistent particle size distribution from nano particles upwards.

One-animal-at-a-time method plus *in vitro* capabilities reduces, refines & replaces animals.

The aerosol switchboard

Three major aerosol generator sources can be alternatively combined with a range of inhalation exposure modules in vitro, ex *vivo,* and *in vivo*

Because the aerosol produced by PreciseInhale is well controlled, it is easily supplied to a range of exposure modules. The aerosol can be sourced from dry powders, clinical inhalers, or nebulized solutions, optimizing conditions for a wide range of substrates.

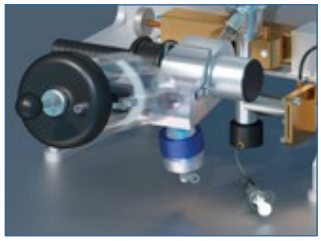
PreciseInhale works as an exposure platform for small-scale inhalation experiments by precisely dosing animals *in vivo*, lungs *ex vivo*, and depositing material for *in vitro* cell culture exposures and dissolution testing.

Dry powder →

Clinical Inhalers →

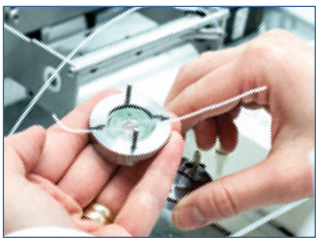
Nebulized solutions →

Isolated Perfused Lung

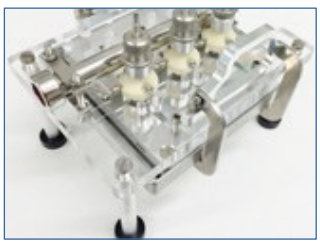


Nose-Only rodents

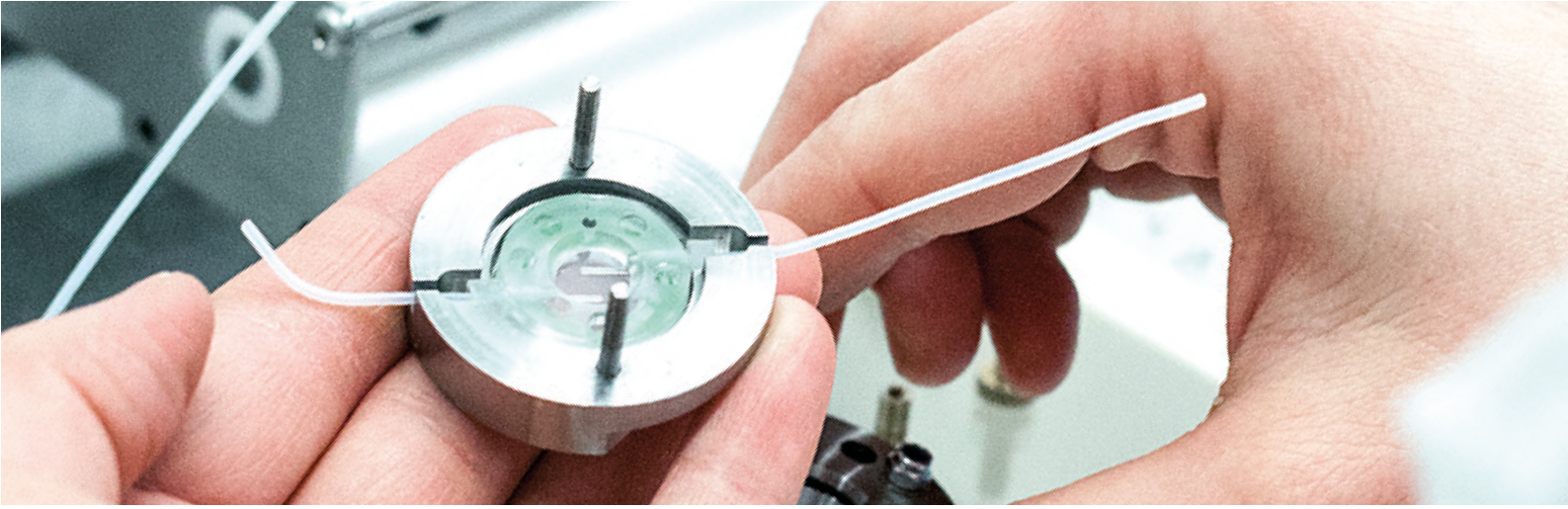
Tracheally intubated rodents



Dissolv*It*®: Artificial air-blood barrier for state-of-the-art absorption and dissolution studies



Xpose*ALI*®: Air-liquid interface cell culture exposures

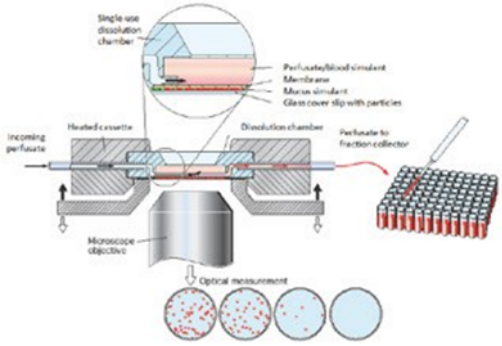


DissolvIt®

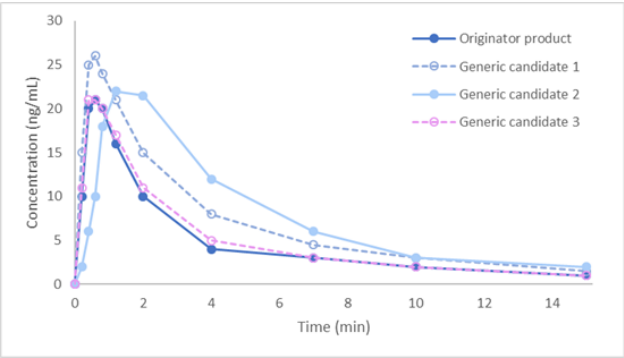
In vitro simulation of dissolution and absorption of drug particles in the lung.

With the DissolvIt the dissolution and absorption of drug particles in the lung can be simulated in greater detail and higher time resolution. In the patented DissolvIt in vitro module dry powder particles are evenly deposited on a glass surface by PreciseInhale. The particles are then brought into contact with a simulated lung/airway mucus and their dissolution and subsequent absorption to a flow-past perfusate (blood simulant) are studied; from the 'luminal' side through optical microscopy and from the 'vascular' side by chemical analysis of the perfusion medium. The system consists of a dissolution chamber, a precision-controlled peristaltic pump and an inverted microscope with a high-resolution camera. The dissolution chamber is perfused in single-pass mode after which the blood simulant is collected in a fraction collector. Operating this artificial lung/blood barrier model delivers unique, and state-of-the-art absorption and dissolution data closely mimicking systemic data from the clinic. In a study funded by the FDA, the DissolvIt™ module was evaluated and, when used in conjunction with a physiologically based biopharmaceutics model (PBBM), demonstrated potential for predicting clinical plasma concentration profiles.

How it works



Ref. Gerde P, et al Assay Drug Dev Technol 2017



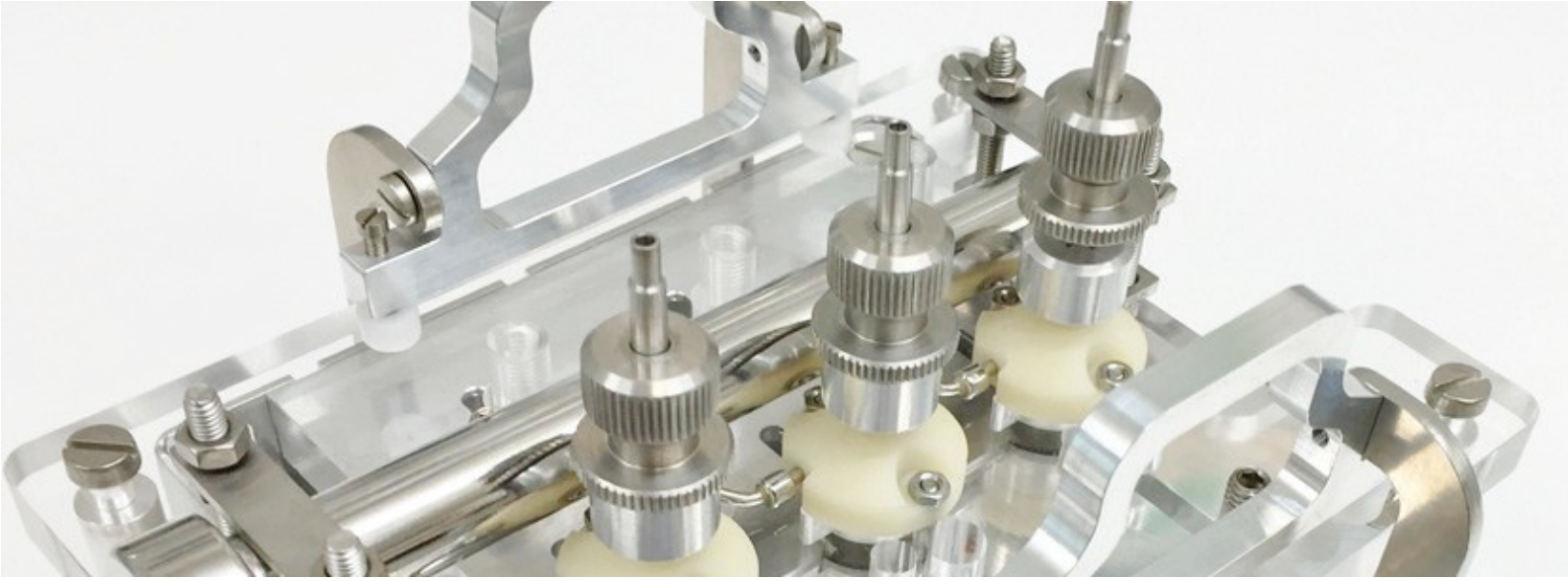
Comparison of three candidate formulations versus originator.

Key features and benefits:

- Ranks substances according to solubility
- Monitors dissolution as well as absorption
- Identifies successful, effective Drug Candidates early on
- Delivers exceptionally detailed data incl. C_{max} and T_{max} curves
- Customizable, programmable Fraction Collector for flexible sampling

"ISAB's in vitro dissolution capabilities are excellent, in fact, leading."

Professor Ben Forbes, King's College London, Institute of Pharmaceutical Science



Xpose*ALI*®

3D *in vitro* cell culture exposure

Xpose***ALI*** 3D cell exposure module combines the aerosol capability of PreciseInhale with 3D cell models cultured at the Air Liquid Interface (ALI). It enables studies of cellular effects induced by airborne particles.

Xpose***ALI*** uses PreciseInhale for exposing cells to respirable size aerosols without the aerosol reaching the cell medium or contaminating the Transwell insert walls. The cells are in contact with the culture medium from below during the entire exposure. After aerosol exposure, the cells are brought back to the incubator for an appropriate time period, so the cellular effects induced by the aerosol exposures can be studied by analyzing the cells, or its medium.

Key benefits and features:

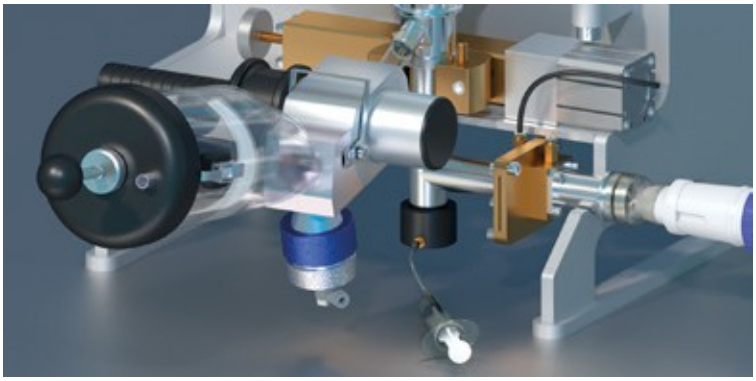
- Lung-like conditions during cell exposure
- Defined aerosol exposure of cells
- Enables studies of cellular effects induced by airborne particles

"Culturing the 3D-models in ALI mimics the uptake of substances in the lung in vivo more exactly than conventional cell culturing. We are confident that XposeALI will play an even greater role in cell culturing research in the future."

Prof. Lena Palmberg, Institute of Environmental Medicine, Karolinska Institutet

In vivo module: Nose-Only inhalation exposures

Nose-only exposures of conscious rodents in restrainer tubes



Key features and benefits:

- Individual exposure monitoring & dosing
- Low inter-individual variability of exposures, typically less than ±10% SD in rats
- Low substance consumption
- Optimal for repeated exposures

The module for Nose-Only inhalation exposures of rodents, one-at-a-time, to respirable aerosols by PreciseInhale makes it possible to reduce Standard Deviation, obtain consistent and highly reliable, PK data and is of particular benefit when repeated exposures are required.

PreciseInhale reduces both the variability of exposure between animals, and test substance consumption—due to individual precision dosing. It allows the study of the distribution of inhaled drugs to blood and other tissues, as well as metabolism and clearance.

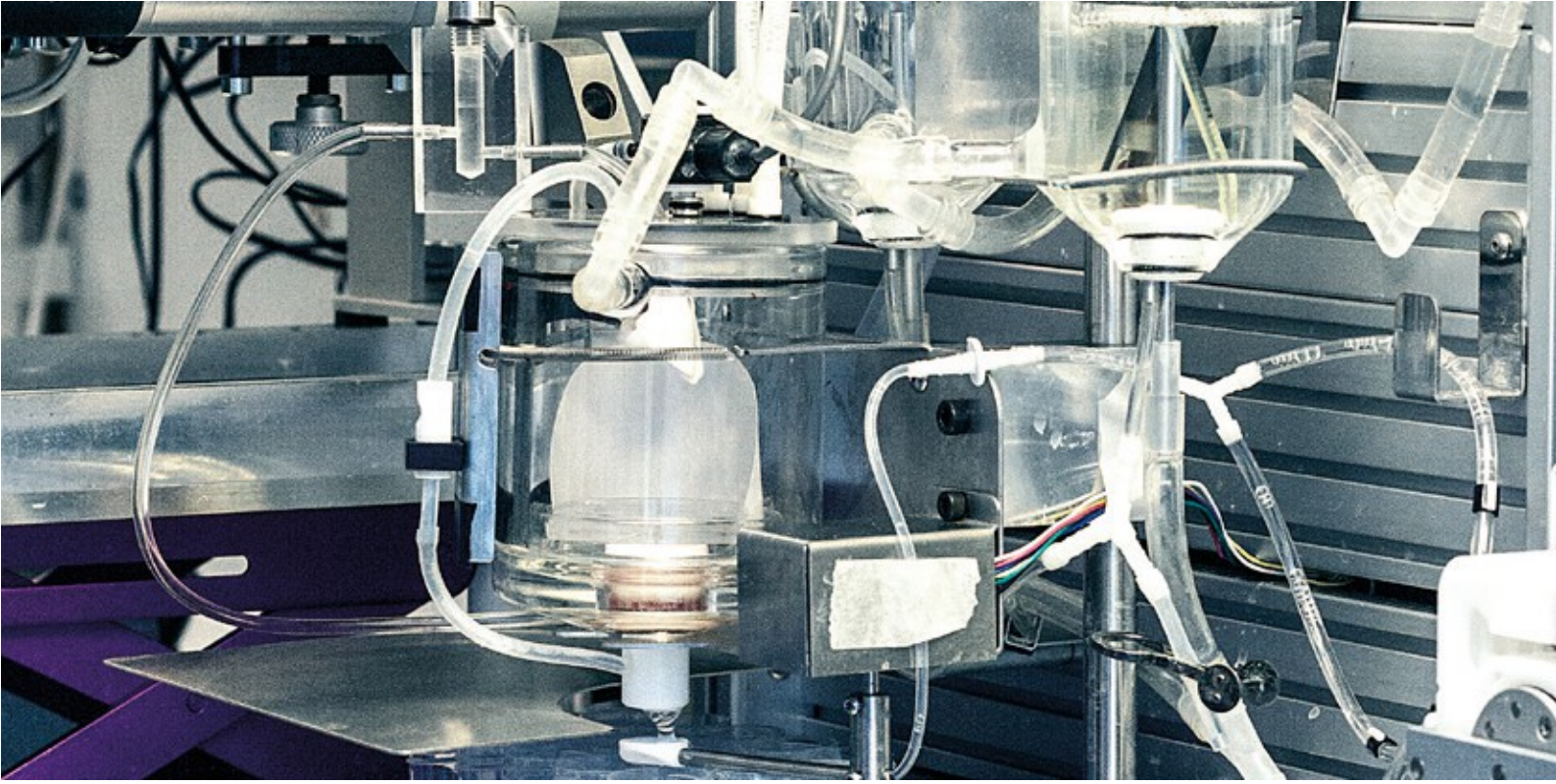
In vivo module: Intratracheal inhalation exposures

Key features and benefits:

- Active control of the dose delivered
- Particle Size Distribution in the lungs closely resembling clinical data
- Eliminates substance losses in the nose
- Low substance consumption
- Reduces and refines the number of animals used in research
- Variability in dosing typically less than ±10% SD in rats

The intratracheal inhalation exposure (IT) module bypasses the nose and provides direct inhalation dosing of the lung in anesthetized rodents.

Avoids substance losses in the nose, including the secondary gastro-intestinal exposures thereof. Produces Particle Size Distribution closely resembling that obtained during clinical inhaler exposures. Enables study of the distribution of inhaled drugs to blood and other tissues, as well as metabolism and clearance. By combining data from IT and IPL exposures to the same aerosol, lung specific PK and systemic PK data from identical IT exposures can be integrated into a full PBPK model of unprecedented detail.



Isolated, ventilated and perfused lung

Ex vivo module for measuring the specific lung PK of inhaled drugs in high resolution

This isolated ventilated and perfused lung (IPL) system is a specially tailored version for delivery of respirable aerosols produced by the PreciseInhale platform to mechanically ventilated rat lungs. The IPL module repeatedly delivers lung deposited doses with a low standard deviation of typically <10%. The result will be lung-specific PK data in high resolution.

IPL is a well-established experimental model in toxicological and pharmacological studies. With this model of IPL it is possible to study the effects of different agents in an intact organ, with physiological cell-to-cell contacts and a native intracellular matrix. It enables the study of lung-specific effects of toxicants and drugs, as it does not involve recirculation of blood from distal compartments. Additional aspects of lung physiology like airway resistance, vascular resistance and gas exchange can be monitored at the same time.

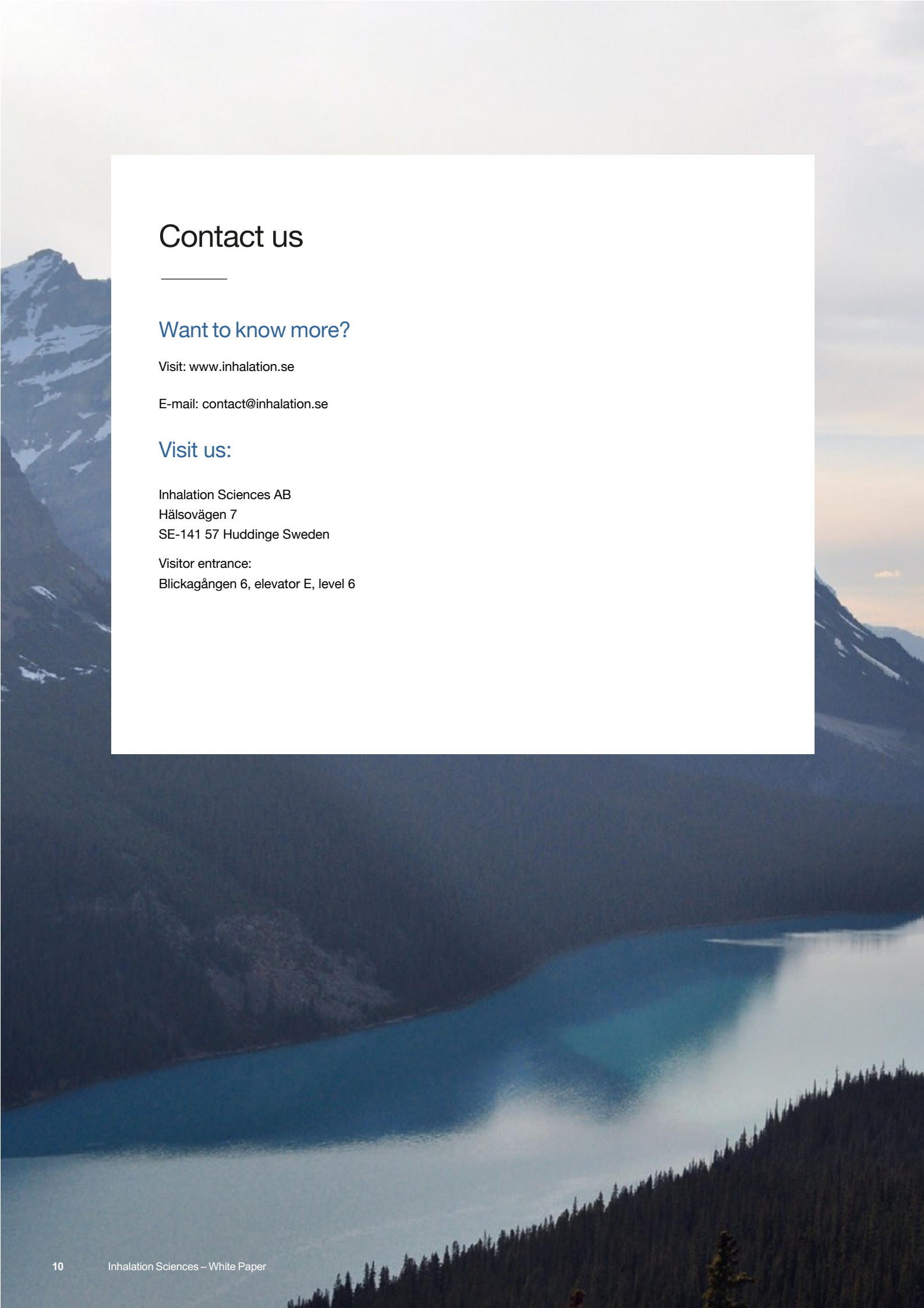
The IPL perfused in a single pass mode is especially advantageous for PK studies of inhaled drugs and toxicants. In our tailored IPL system, the perfusate is collected throughout the perfusion period using a fraction collector, which also makes it possible to monitor the perfusate flow rate. The perfusion system can also be converted to recirculation mode to facilitate detection of an accumulating substance or its metabolites in a smaller perfusate volume.

Key features and benefits:

- Characterization of lung absorption and retention in detail (up to 2 hr sample collection).
- Less than 10% variability during repeated dosing.
- Total mass balance control, no losses.
- Detect possible acute organ toxicity at the earliest time points.

Clinical exposures of human volunteers

In a clinical feasibility study, it was shown that the PreciseInhale can be used to substantially improve dosing precision of inhaler aerosols and also to direct exposures of such aerosols to different major regions of the lung, so called regional targeting. This is a modification of the exposure module used in preclinical exposures of large animals such as pigs and dogs.



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