

## *Using multiscale mechanism based mathematical modeling to address many of the challenges associated with the estimation of local lung concentration after inhaled drug delivery*

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**Background/Objectives:** Mathematical modeling can help provide otherwise unavailable information on of the local drug concentration in target tissues of the lung for multiple species. The aims of this work were to use the physicochemical properties and the drug delivery details as input to implement the following objectives:

- Multiscale mechanism-based integrated computational platform developed to provide mechanistic insights into key complex species-specific physiological-based processes associated with pulmonary drug delivery.
- Model qualification using existing lung and systemic data from the literature.
- Effect of breathing patterns on lung deposition and PK.
- Translation of systemic and lung PK from preclinical species to humans using in-silico lung platform.
- Effect of physicochemical properties on lung selectivity.
- Coupling of the systemic and lung PK to their associated local effects.

**Methods:** Five different mathematical modules were integrated in the platform: deposition, dissolution, transport, distribution, and effect. The inhaled modeled particles will be deposited [1] into three main regions of the respiratory tract: the upper tract, tracheobronchial region, and pulmonary region. Once deposited in the different lung regions a dissolution module accounts for the particles dissolving [2] in the surface lining fluid while simultaneously being cleared from the airway region (generation 0 to 15) due to the action of the mucociliary escalator. The dissolved drug partitions into seven different lung tissue compartments before reaching the systemic circulation [3]. A PBPK module [4] accounts for the drug distribution, partition throughout the body, and elimination. A mechanism specific PD module was used to account for the effect of corticosteroids and inhale soluble guanylate cyclases. The model was qualified using deposition fraction (DF) and PK data from diverse compounds in rats, dogs, and humans. For each case, the input data for the model included the drug physicochemical properties while the PK clearance parameter was either estimated based on the data or used from literature, if available. Single dose data then was used to test the agreement of the model with the observed PK profile in the systemic circulation for rats, dogs, and humans

**Results:** A translational strategy from rats to humans was done using the exact same compound specific physicochemical properties, allometrically scaled clearance, and the species specific dose delivery information. Good agreement was obtained between the predicted PK and the systemic concentrations for rat, dogs, and humans for the compounds tested after a single inhaled dose. The lung concentrations predicted were at least two orders of magnitude higher than the corresponding systemic concentration during the drug terminal decay phase. PD predictions were in agreement with available data.

**Conclusion:** The lung modeling platform presented here provided an in-silico option to overcome many of the challenges related to the estimation of the local drug concentration in the lungs. It was qualified using existing inhaled literature deposition data and systemic PK data for multiple species

(rat, dog, human). This platform demonstrated the ability to make PK/PD translation between species using the exact same compound specific physicochemical properties with allometrically scaled clearance underlining the value of this tool as a translational platform to make accurate human projections from preclinical observations.

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**References:**

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