



Informing sampling design for lung distribution studies using a pulmonary population PBPK model

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1. Introduction

Understanding intrapulmonary PK following inhalation remains a significant challenge in drug development for lung delivery. Accurate assessment of drug concentrations at the site of action, particularly in the epithelial lining fluid (ELF), is crucial for evaluating therapeutic efficacy. Current lung sampling methods include bronchoalveolar lavage (BAL), biopsies, and the more recent bronchosorption technique, which enhances regional specificity while reducing potential quantification errors [1].

2. Aims

This study aimed to develop a pulmonary population PBPK model for inhaled salbutamol in order to:

- evaluate different sampling techniques for their ability to estimate key lung PK parameters
- assess sampling strategies for hypothetical drugs with varying physicochemical properties
- inform lung PK sampling methodologies applicable to a broader range of inhaled compounds

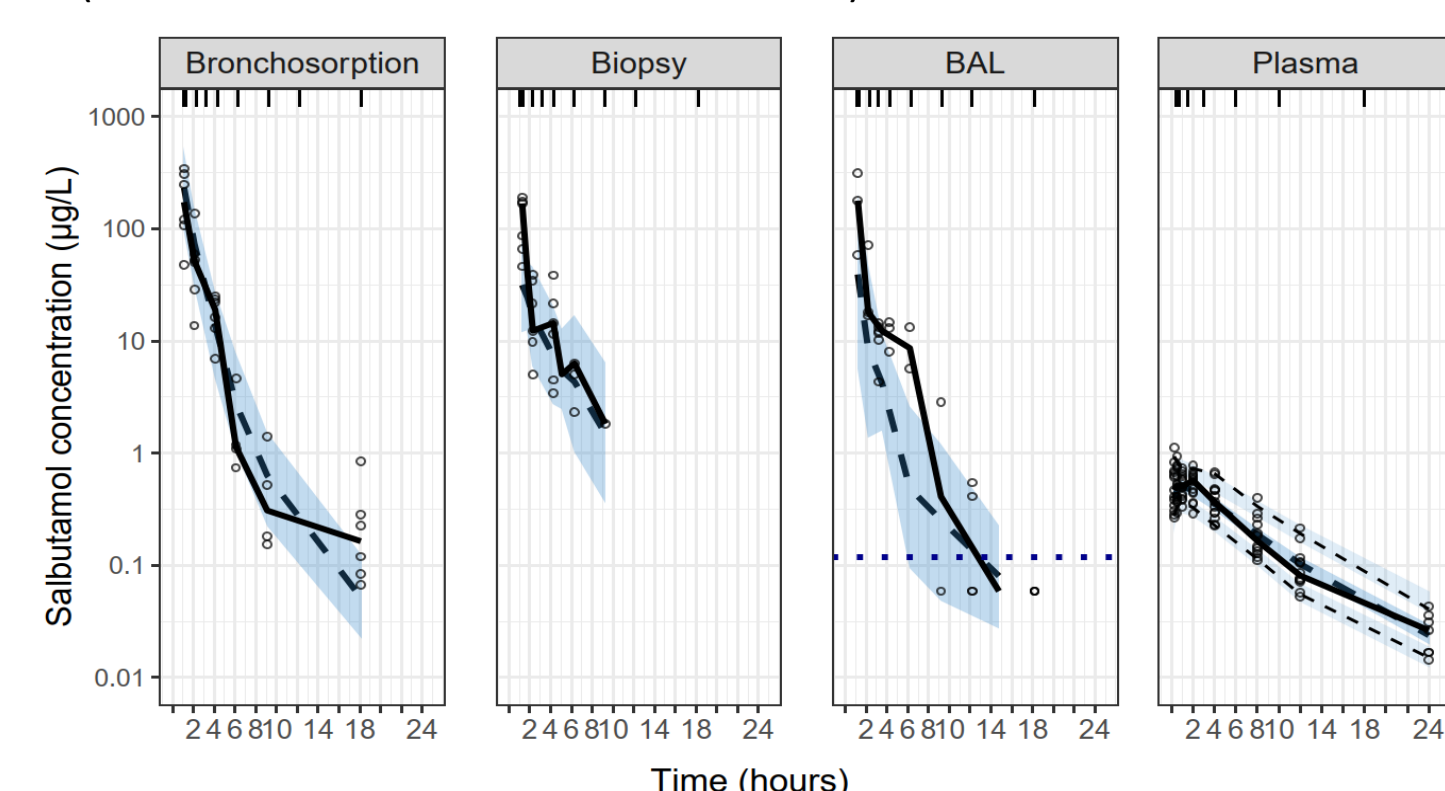
6. Take home message

- Estimates of lung-specific parameters such as $K_{p,u,lung}$ and P_{eff} are technique-sensitive
- Optimal sampling timing varies with drug permeability:
High-permeability drugs → early sampling
Low-permeability → later or broader windows

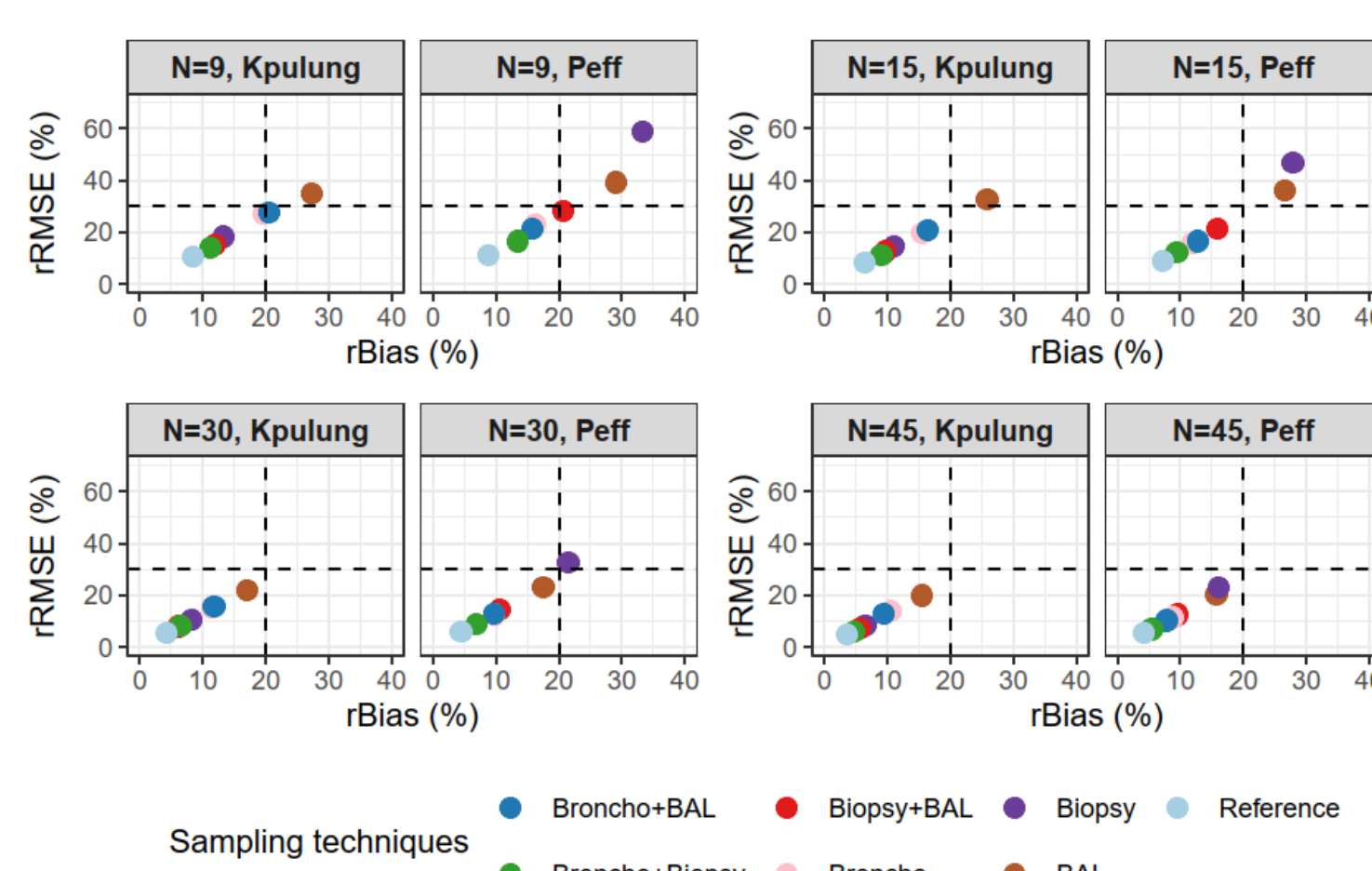
4. Results

- The minimal PBPK model estimated the $K_{p,u,lung}$ and P_{eff} of salbutamol to 11.0 and 0.543 m/hour, respectively.
- BSV was significant in clearance and for the lung disposition fraction (F1), with estimates of 19% and 129% (CV), respectively. BSV was not significant for $K_{p,u,lung}$ and P_{eff} .

Visual predictive checks of the population PBPK model of salbutamol (blue dashed line stands for LOQ of BAL)



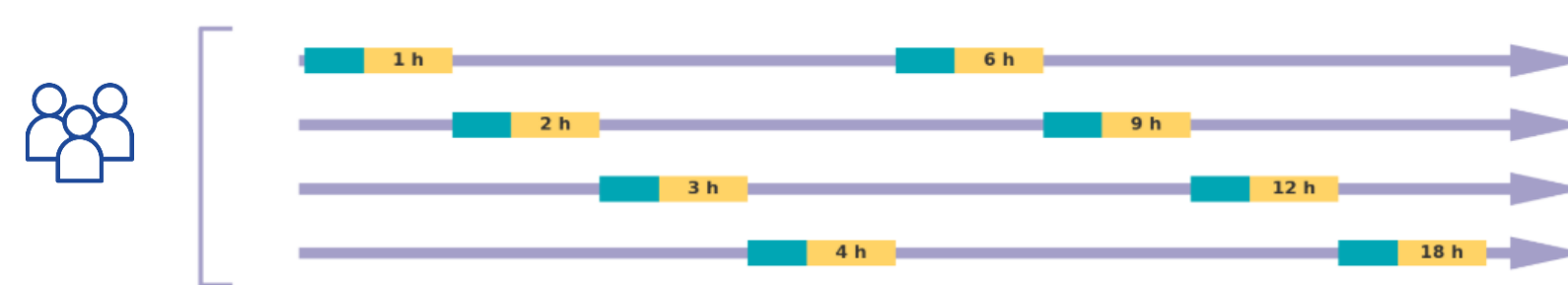
Bronchosorption outperformed BAL and biopsy as single-technique approach; bronchosorption plus biopsy demonstrated the best performance among two-technique combinations



3. Methods

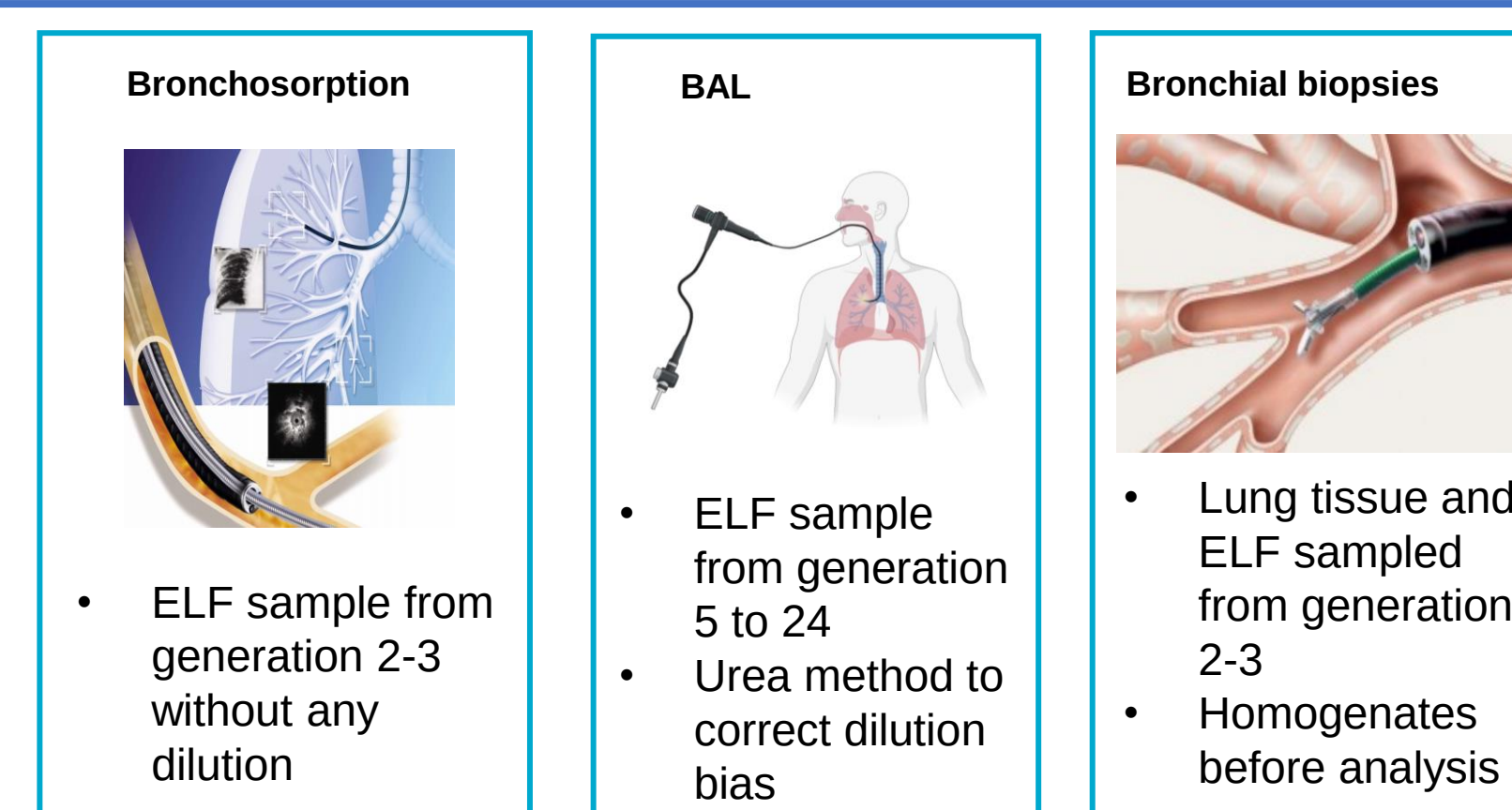
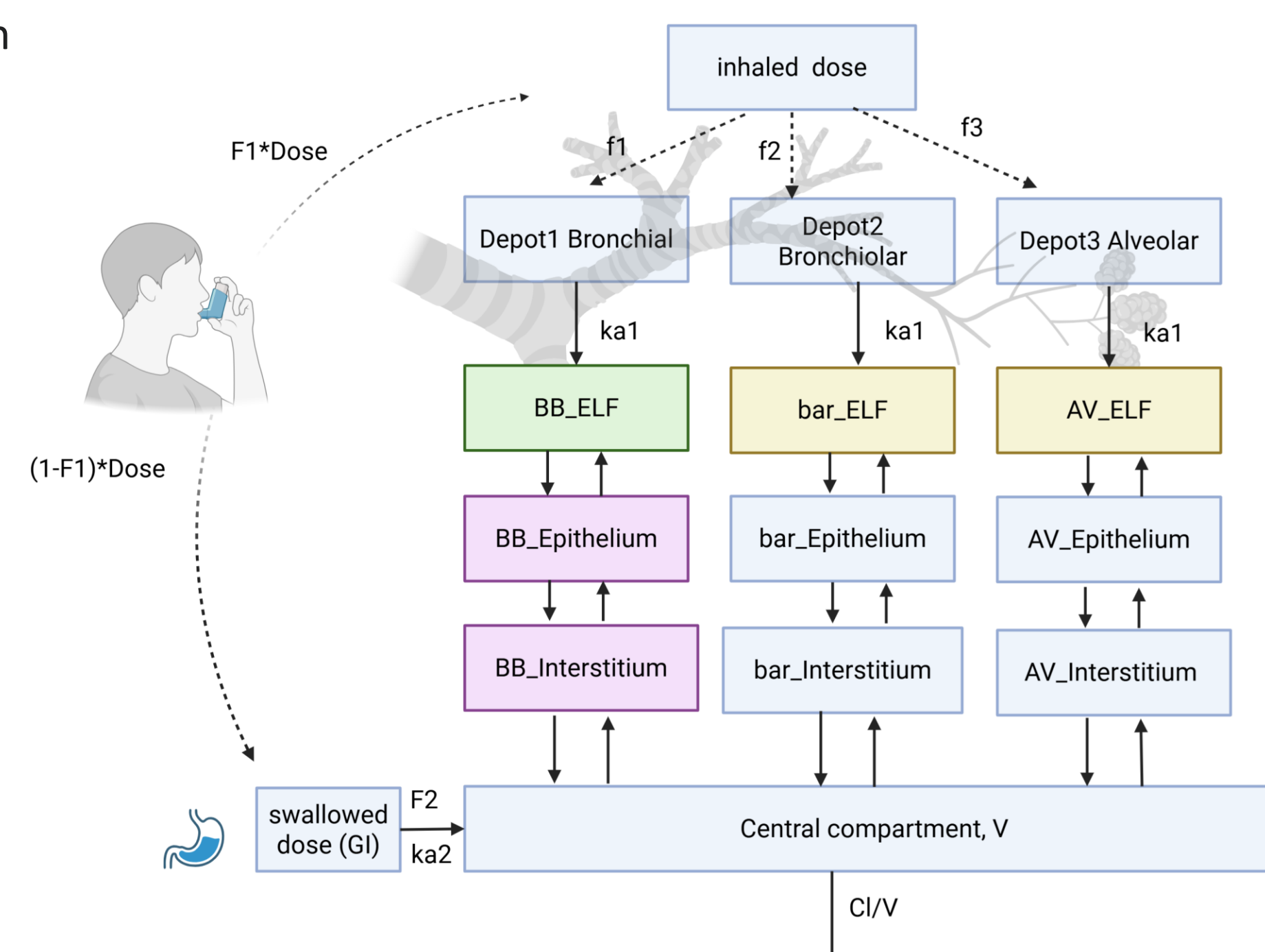
Study design and sampling techniques

- Secondary analysis of a published clinical pharmacokinetic (PK) study (NCT03524066) [1].
- 13 healthy adult volunteers inhaled a singled dose of salbutamol. A staggered pulmonary sampling design was applied.



- Two bronchoscopy-assisted lung sampling sessions per participant
- Subjects were divided into 4 groups with different sampling schedules
- In each sampling session, sequential lung samples were taken as follows: 2 bronchosorptions, 1 BAL, 2 mucosal biopsies. Plasma samples were collected at 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose

Population-based minimal PBPK modeling



- Three sampling techniques were applied for sampling at different regions of the lung;
- A total of 101 plasma and 100 lung PK samples were collected.
- The M3 method was applied for BLQ of BAL data [2]. For other observations, BLQ were ignored

- The **plasma PK model** was based on a previous publication [3], which separates lung and gut compartments for dual absorption pathways, linked to a one-compartment PK model.

- The **lung PBPK model** divided a human lung into three regions: trachea and bronchial (generation 1 to 9), bronchiolar (generation 10 to 16), and alveolar region (generation 17 to 24), which is a reduced version of our previous published model [4]. Key lung parameters were $K_{p,u,lung}$ and P_{eff} .

- BSV were investigated on plasma PK parameters, $K_{p,u,lung}$ and P_{eff} .

Simulations and evaluations of sampling designs

- Pulmonary PK profiles of hypothetical compounds with P_{eff} set to 10 times higher, 10 times lower, and 100 times lower than that of salbutamol were simulated.
- Stochastic simulations and estimations were used to understand:
 - Impact of sampling techniques, alone or combined, for estimation of $K_{p,u,lung}$ and P_{eff} .
 - Impact of different limited sampling strategies for estimation of $K_{p,u,lung}$ and P_{eff} for drugs with different permeabilities.

5. Limitations

- The study was limited by its sample size and well-controlled population;
- extrapolation from the current model results to a diseased population was not addressed

ABBREVIATIONS

BAL, bronchoalveolar lavage; BSV, between subject variabilities; ELF, epithelial lining fluid; CV, coefficients of variation; $K_{p,u,lung}$, unbound lung-to-plasma partition coefficient; P_{eff} , effective permeability; PK, pharmacokinetics; PBPK, Physiologically based pharmacokinetic; BLQ, below the limit of quantification; LOQ, limit of quantification; rBias, relative absolute bias; rRMSE, relative root mean square error.

Acknowledgments

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