

The physiological interpretation of population pharmacokinetic modelling results for inhaled olodaterol

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Background and Objectives

- A previously developed inhalation pharmacokinetic (PK) model described the PK of an inhaled olodaterol solution, administered utilizing a Respimat®, with three parallel absorption processes, s. Tab. 1 [1].
- A computational fluid dynamics (CFD) model (Fig. 1) predicted a pronounced peripheral deposition of another drug (tiotropium) inhaled utilizing a Respimat®.
- The inhalation PK model (Tab. 1) indicated a more central deposition of the drug when associating the slow absorption process to the central airways and the fast absorption process to the alveoli.

→ Discrepancy between CFD predictions and PK estimates.

Tab. 1: Estimated lung absorption characteristics of the inhalation PK model [1].

Absorption process	Fraction [% of lung dose]	Absorption rate constant [1/h]
Slow	70.9	0.0144
Intermediate	24.2	0.249
Fast (non-smoker)	4.9	1.79
Fast (smoker)	4.9	3.80

- A possible explanation for the deposition discrepancy and the long half-life ($t_{1/2} = 48.1$ h) of the slow absorption process after inhalation might be lysosomal trapping. However, even though lysosomal trapping should also happen after IV administration, a comparable half-life was not observable in the plasma concentration-time profile after IV.

→ To test the hypothesis of a slow systemic distribution process (potentially lysosomal trapping) urine data was integrated into a new population PK analysis.

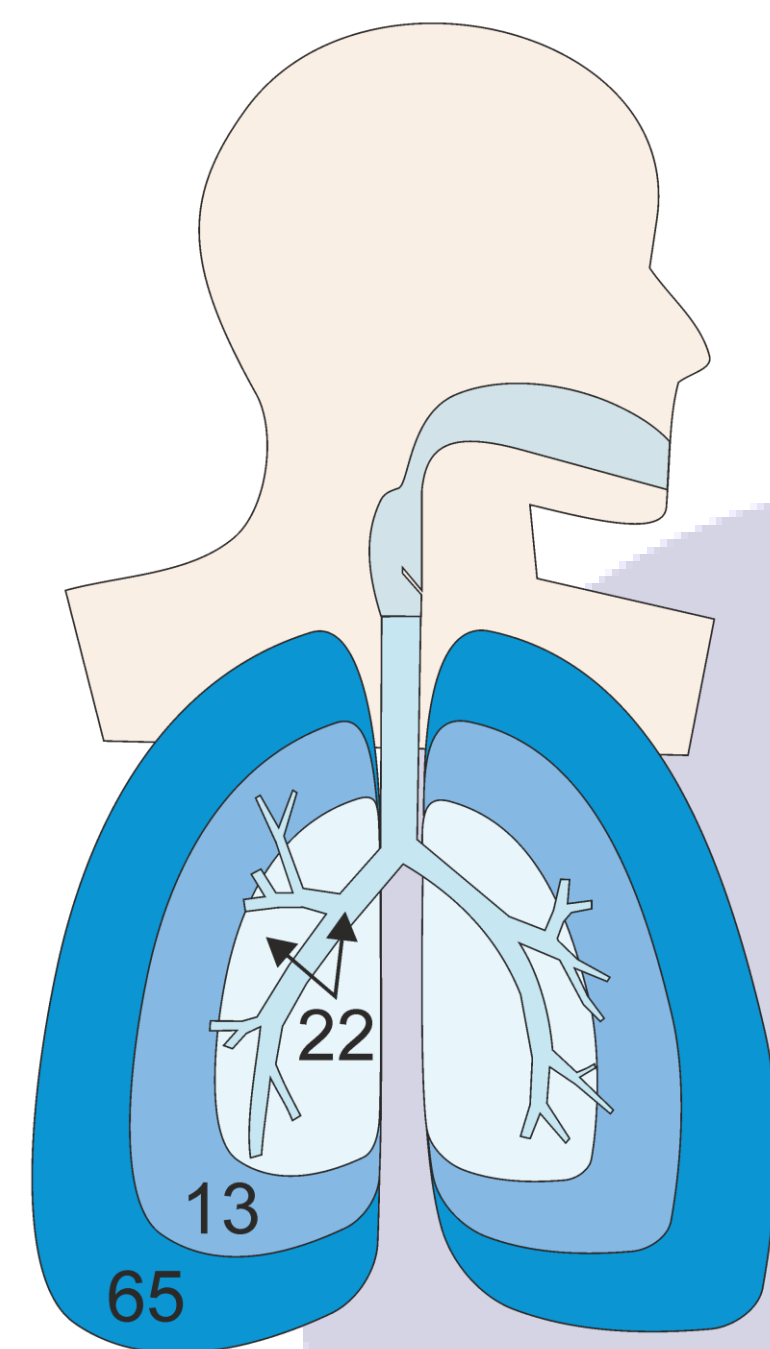


Fig. 1: % of the lung dose in different airway generations (G): Trachea-G14 (dark blue), G15-20 (blue), G21-alveoli (light blue) obtained from a CFD study under turbulent air flow conditions; adapted and modified from Ciciliani et al. [2].

Methods

Data

- Three trials in healthy volunteers (HV): IV (urine, plasma data), inhalation (plasma data) (Tab. 2).

Model Development

- IV: Compared to the previous approach [1] additional urine data was used for IV PK model development → more accurate characterisation of the terminal phase of the plasma concentration-time profile.
 - Inhalation: Structural parameter estimates and interindividual (IIV) parameter estimates of the IV model were fixed and different absorption models were investigated: i) single absorption process ii) two to four parallel absorption processes iii) transit absorption model.
- Model selection was based on several criteria, such as goodness-of-fit (GOF) plots, precision of parameter estimates, and the changes in OFV.

Tab. 2: Dosing and sampling details of clinical trials.

	Inhalation	Intravenous
Dose	2.5 µg to 70 µg	0.5 µg to 25 µg
Number of HV with PK samples above LLOQ	Total: 84	Total: 48
Plasma samples above the LLOQ	N = 1152 TAD: 0.03 h to 96 h	N = 435 TAD: 0.03 h to 24.1 h
Urine samples above the LLOQ	Not evaluated	N = 231 (TAD: 3.53 h to 96 h)

- References:**
- [1] JM Borghardt, B Weber et al. In Proceedings of Respiratory Drug Delivery 2014 Book 2: 417 (2014)
 - [2] AM Ciciliani, H Wachtel et al. In Proceedings of Respiratory Drug Delivery 2014 Book 2: 453 (2014)
 - [3] P Casarosa, I Kollak, J et al. Pharm Exp Ther J 337: 600 (2011)
 - [4] AC MacIntyre, DJ Cutler et al. Biopharm Drug Dispos J 9:513 (1988)

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Results

1) Final IV model:

- Four compartment (CMT) systemic disposition model with two parallel clearance processes from the central CMT; renal (CL_R) and non-renal (CL_{NR}) (Tab. 3, Fig. 2-3, 6).

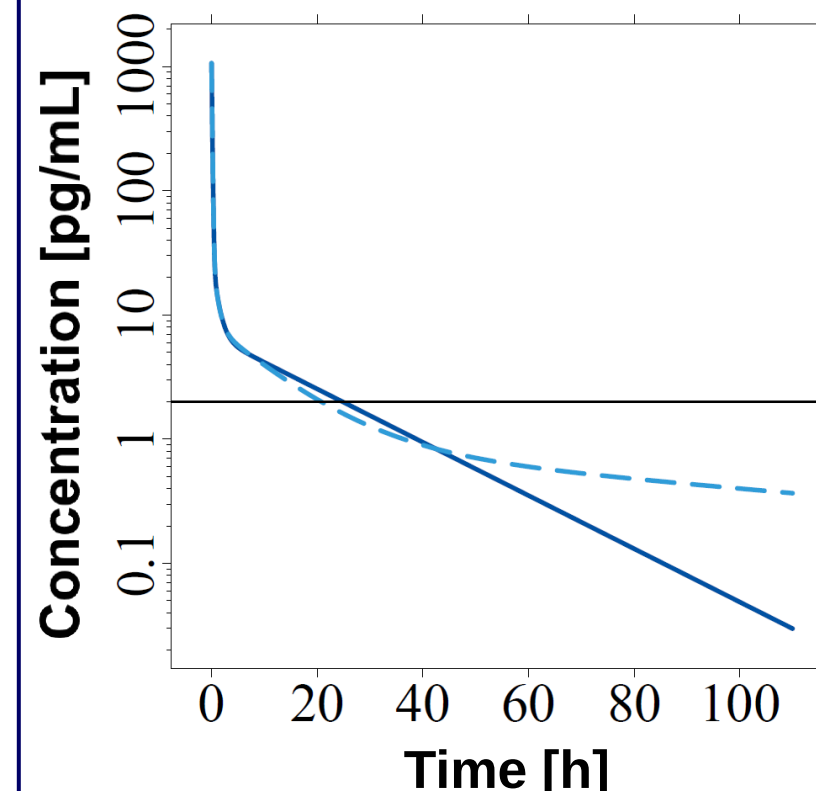


Fig. 2: Simulation of a typical plasma concentration-time profile after IV bolus of 25 µg. Dark blue profile: Prediction of the previous 3 CMT IV model [1]; light blue dashed profile: Prediction of the 4 CMT IV model; black line: Lower limit of quantification.

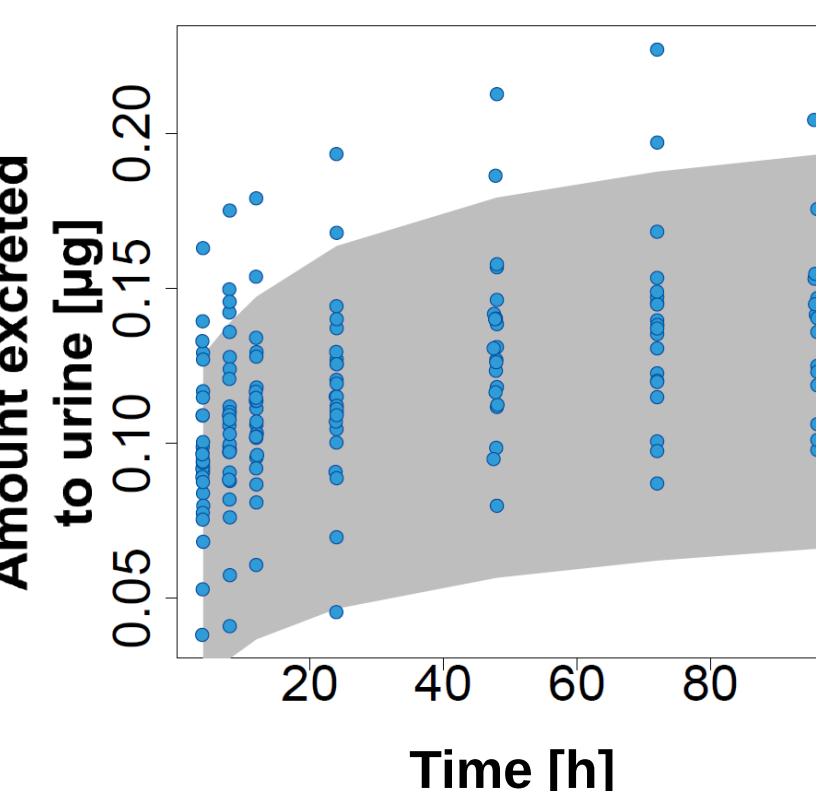


Fig. 3: Dose-normalized visual predictive check of the amount excreted to the urine after IV administration of olodaterol (infusion time: 0.5 h). Grey shaded area: 90% prediction interval; black line: Lower limit of quantification.

- The terminal half-life was 82.4 h compared to 14.0 h of the previously developed three CMT disposition model (no urine data).

2) Final inhalation model:

- Structural model is presented in Fig. 6 and parameter estimates in Tab. 3 (GOF-plots: Fig. 4-5).
- Longer terminal half-life of the IV model and an increased estimate of k_{a_Slow} (compare Tab. 1 and Tab. 3) demonstrated the absence of flip-flop kinetics present in the inhalation PK model without IV urine data [1].

→ Long terminal half-life was mainly caused by a slow distribution process.

- The slow distribution ($k_{54} = 0.0122/h^{-1}$) and slow absorption process accounted for different magnitudes of the dose (16.3% and 74.8%, respectively).

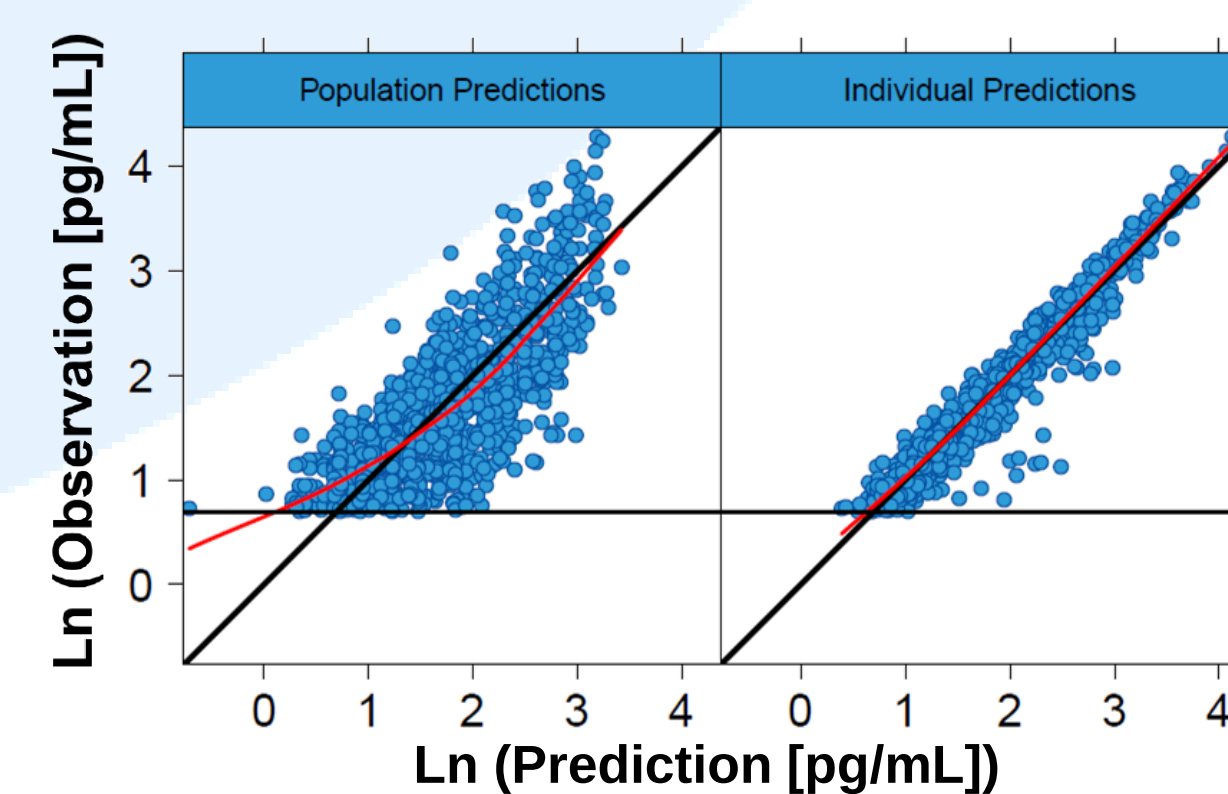


Fig. 5: Ln-transformed observations plotted versus Ln-transformed (individual) predictions. Red lines: Locally weighted scatter plot smoothing lines; black lines: Lines of identity.

Tab. 3: Estimated PK parameters of the final IV and inhalation PK model.

PK Parameter	Estimate (RSE, %)	IIV (% CV)
V4*	23.5 L (4.3)	26.2
V5*	2590 L (36.0)	-
V6*	474 L (10.6)	-
V7*	16.1 L (19.8)	-
Q5*	31.7 L/h (12.3)	25.7
Q6*	65.7 L/h (5.20)	16.8
Q7*	22.5 L/h (8.09)	-
CL _R *	10.5 L/h (4.58)	-
CL _{NR} *	63.7 L/h (8.48)	26.9
Lung dose (LD)	0.517 (5.55)	36.15
k_{a_Slow}	0.0256 h ⁻¹ (10.0)	32.8
F_{Slow}^{*2}	74.8% LD (2.14)	13.5
k_{a_Int}	0.369 h ⁻¹ (8.89)	-
F_{Int}^{*2}	21.3% LD (3.13)	29.2
k_{a_Fast} (Non-Smoker)	2.20 h ⁻¹ (10.7)	-
k_{a_Fast} (Smoker)	4.98 h ⁻¹ (11.0)	-
$F_{Fast}^{*2/+3}$	3.9% LD	58.5
$\sigma_{proportional}$	17.2% CV (1.66)	-

*Parameter estimates based on IV data
²Fraction of the lung dose
³Structural and IIV parameter were not estimated but calculated with the other parameters.

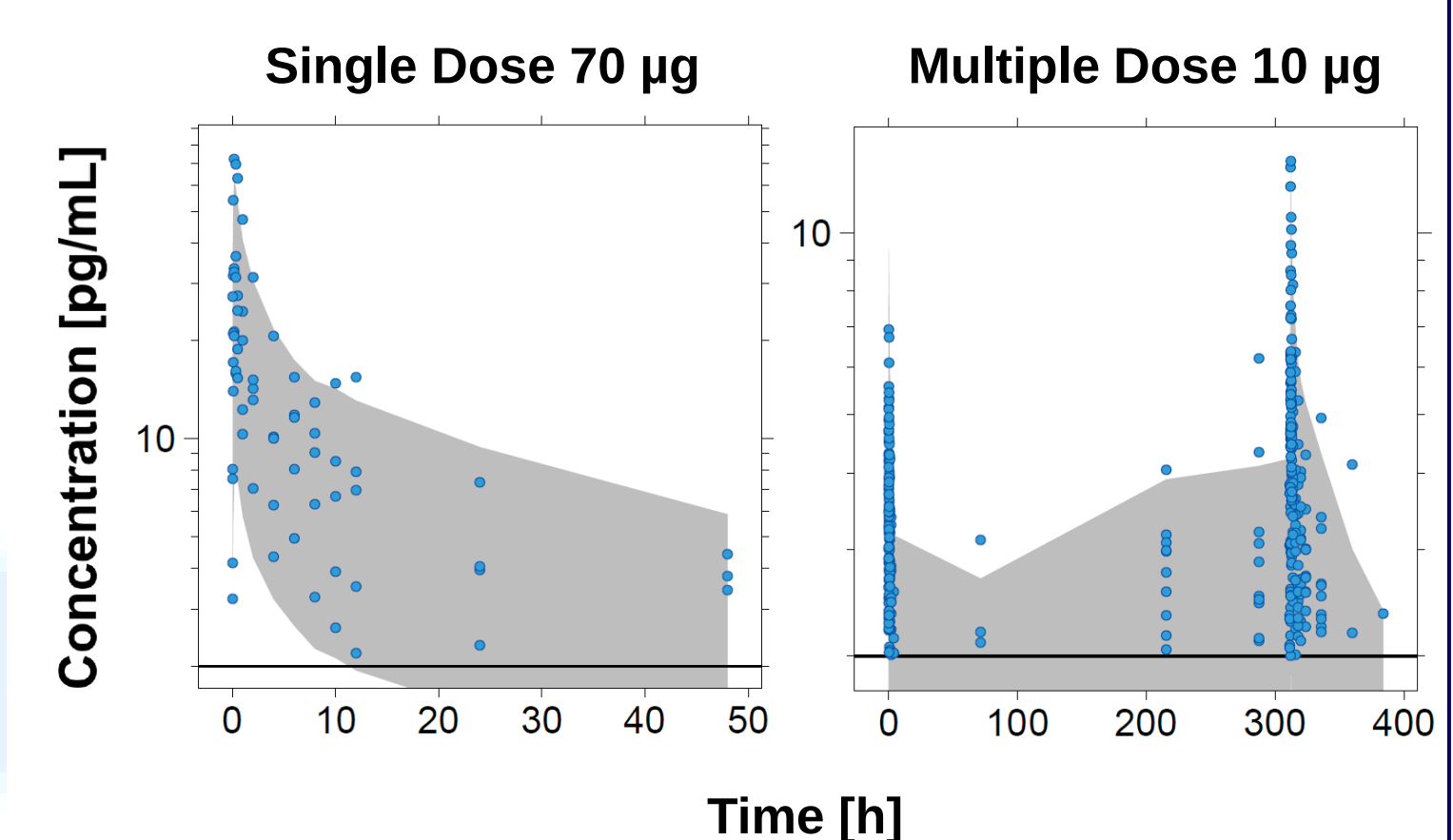


Fig. 4 a-b: Visual predictive checks of the PK model describing single (left plot) and multiple (right plot) olodaterol inhalation of different doses on a semi-logarithmic scale. Grey shaded area: 90% prediction interval; black line: Lower limit of quantification.

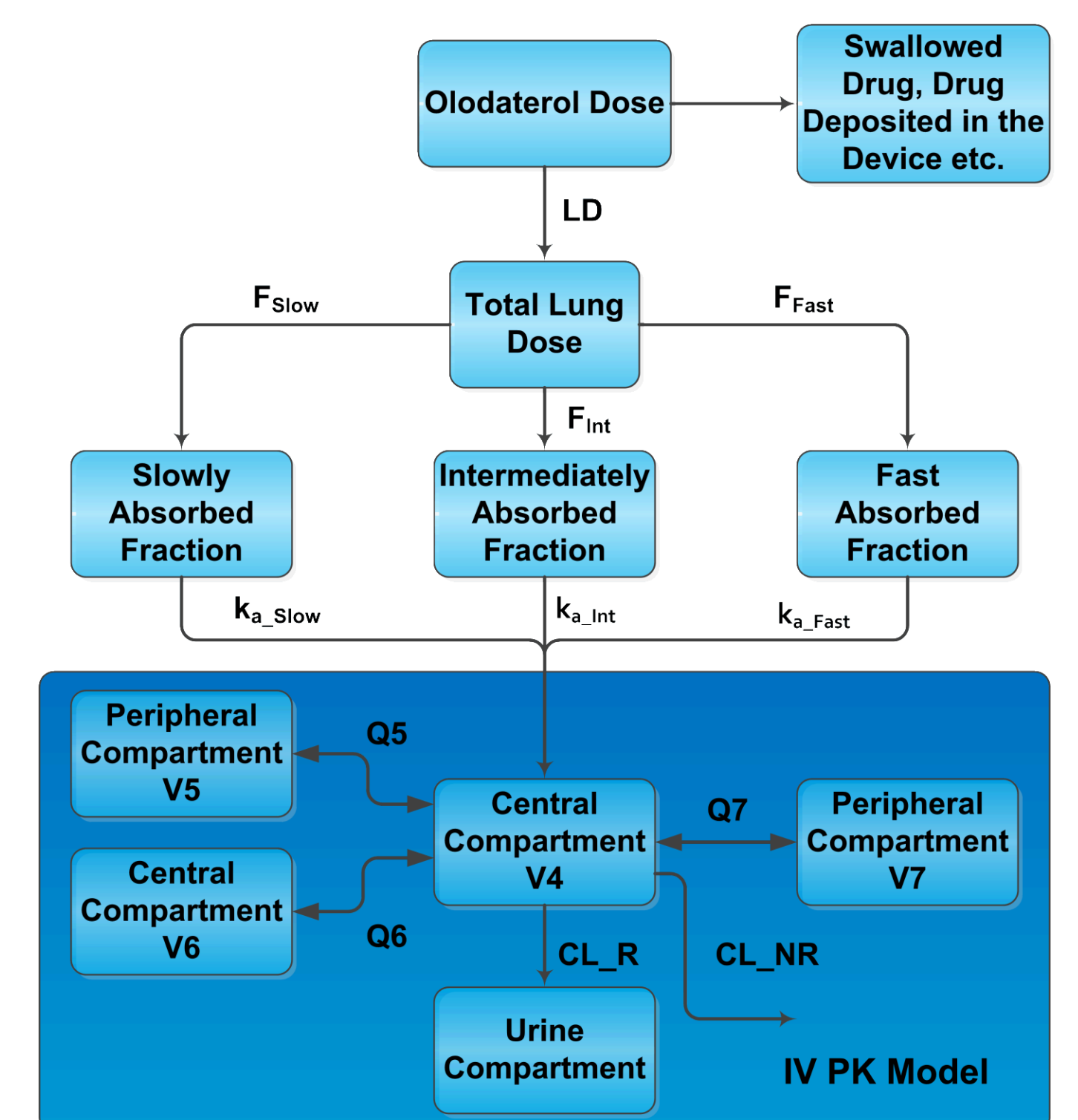


Fig. 6: Schematic illustration of the final population PK model. Lower part of the illustration: IV PK model; upper part of the illustration: Inhalation PK model; LD: Lung dose; F: Fraction of the lung dose absorbed; k_a : Absorption rate constant; CL_R: renal clearance; CL_{NR}: Non-renal clearance; V: Volume of distribution; Q: Inter-compartmental clearance.

Discussion and Conclusions

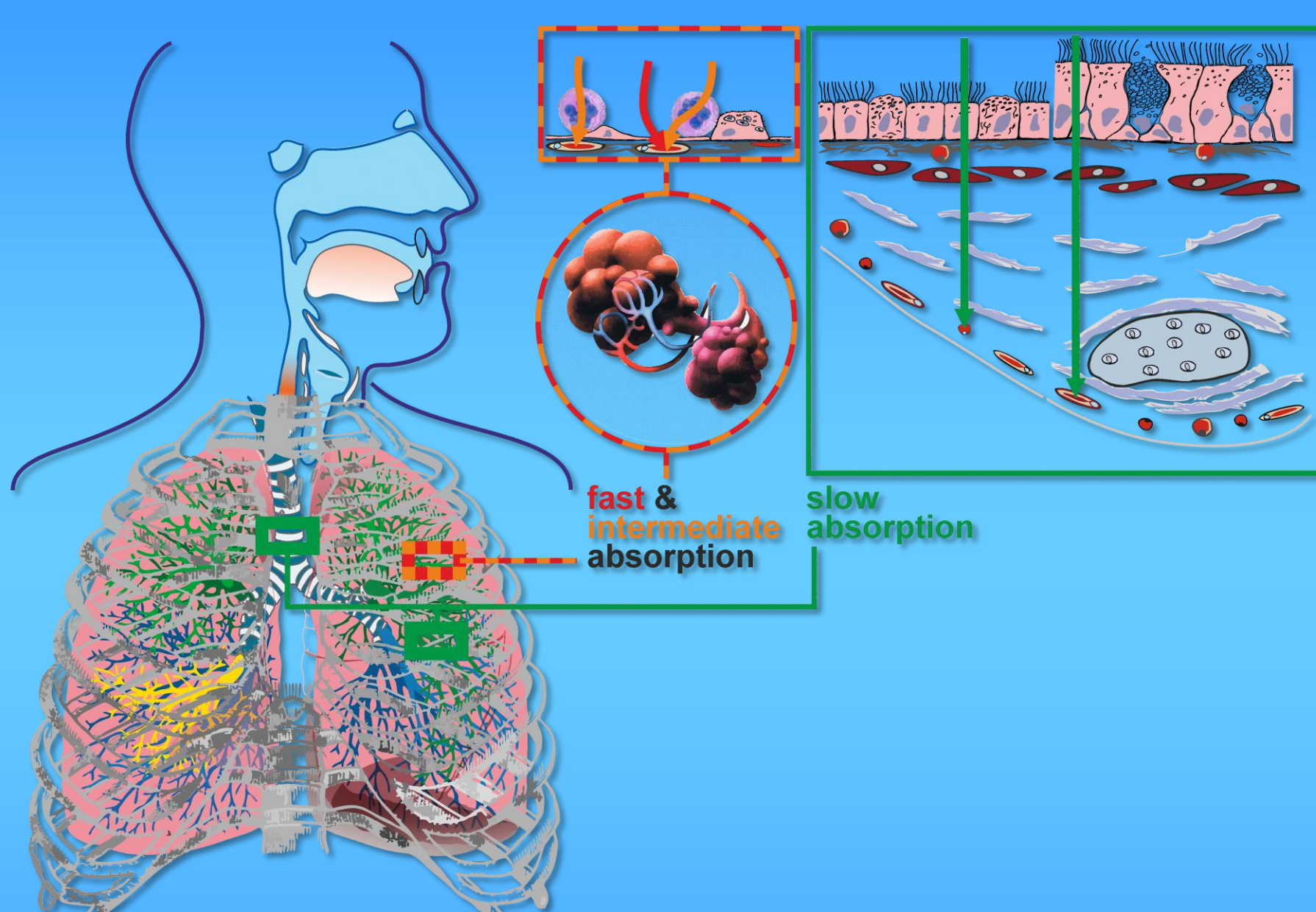


Fig. 7: Simplified structure of the human airways. Green arrow: Absorption of drug deposited in the conducting airways, orange arrow: Indirect absorption (after lysosomal trapping) of drug deposited in the alveolar space, red arrow: Direct absorption of drug deposited in the alveolar space.

- The modelling results demonstrated that three parallel pulmonary absorption processes are necessary to accurately describe the PK of inhaled olodaterol. Furthermore, the benefit of including urine data after IV dosing to better characterise the terminal half-life was demonstrated.
- The results obtained support the hypothesis of a slow systemic distribution process that is relevant after IV dosing of olodaterol and not specific for olodaterol inhalation. A likely process due to drug characteristics (basic character of olodaterol [3]) and lung characteristics (high amount of lysosomes [4]) is lysosomal trapping. This aspect may also explain that a high fraction is slowly absorbed if the drug is directly administered to the lysosome rich lung, compared to the low relevance of the slow distribution process after IV dosing.
- Assuming lysosomal trapping, the three different fractions absorbed might be interpreted as absorption to the plasma from only two areas of the lung. **Slow absorption (after lysosomal trapping) in the conducting airways, intermediate absorption might represent indirect (after lysosomal trapping) absorption in the alveolar space, and fast absorption might represent direct absorption in the alveolar space** (Fig. 7). Associating two absorption processes instead of only the fast process to the alveolar space might also explain most of the discrepancy between predicted deposition patterns (CFD) and the estimated absorbed fractions (PK model).
- Additional *in vitro* / *ex vivo* assays should be performed to evaluate this hypothesis and to further increase the understanding about possible PK characteristics after drug inhalation.